Cannabis

Effects of consumption on health

This document presents the summary and recommendations of an expert group set up by INSERM (Institut national de la santé et de la recherche médicale, French Institute of Health and Medical Research) under their collective expertise procedure, to answer questions raised by MILDT (Mission interministérielle de lutte contre la drogue et la toxicomanie, Interministerial mission for the fight against drugs and drug-dependency) on the effects of cannabis consumption on health.

The Centre d'expertise collective de l'Inserm (Inserm collective expertise centre) has co-ordinated this collective expertise strategy with the DAPS (Département animation et partenariat scientifique, Leadership and scientific partnership department) for the preparation of this dossier in conjunction with the service de documentation du département de l'information scientifique et de la communication (Disc, documentation service of the scientific information and communication department) for the bibliographical research.

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Foreword

Epidemiological data collected in Europe as well as in the United States, Australia or New Zealand reveal an increase in the prevalence of cannabis use among the young.

Although fundamental research studies on the cannabinoids have made substantial progress in recent years, we must acknowledge that there are still gaps in our knowledge of how cannabis use affects health. Data on the various acute and chronic effects of cannabis, based as they are on case reports, clinical studies or at best on retrospective studies, are few or contradictory. It is important to note at the outset how difficult it is to collect population data on an illegal drug.

The Interministerial Mission against Drugs and Drug addiction (MILDT) wanted an overall assessment of the available knowledge on the effects of cannabis use on health, based on an exhaustive analysis of the literature and asked INSERM to undertake this task by means of the collective expertise procedure.

In order to respond to this request, INSERM has set up a multidisciplinary group of scientific experts in the spheres of descriptive and analytical epidemiology, sociology, biology and neurobiology, toxicology and neuropharmacology which also includes clinical or general psychiatrists in clinical practice.

The expert panel group structured its analysis around the following questions:

- What is known about levels of cannabis consumption, about how they change over time and about the characteristics of users, especially young people? Are the changes described in France comparable with those observed in other developed countries?
- What is known about the contexts and modes of consumption? What are the situations in which people experiment with the drug? What is the proportion of regular users and what are their characteristics? What are the significance of polyuse phenomena and pathways of consumption? What is known about the evolution of cannabis supply and channels of distribution in different social backgrounds? What is the connection between consumption and desocialisation or delinquency?
- What are the characteristics of the drug? What are the active principals in the different varieties of cannabis? What is the metabolism of cannabis in humans? What are the biological markers of the presence of cannabis in the organism?
- What are the effects of cannabis on health? What are the neurological effects? Are they reversible? Does cannabis induce dependency? What is known about interactions with other drugs? What is the connection between consumption of cannabis and psychiatric disorders?
- What other effects on health are there, in particular on the respiratory, cardiovascular and immune systems, as well as on fertility and fecundity? What are the data on potential carcinogenic effects?
- What are the results of animal studies? To what extent can they shed light on data collected in humans?
- What are the mechanisms of action of the cannabinoids on the various target tissues?

Over 1 200 articles were selected after searching trough international bibliographic databases (Medline, Embase, Toxibase, Psycinfo and Pascal). Most of the articles are concerned with the

mechanisms of action of the active principle of cannabis, Δ9-THC, in relation with the endocannabinoid system. A certain number of the animal studies are already outdated and particular attention was paid to the most rigorous recent studies. As regards human data, all the studies (case reports, case control studies, retrospective studies) were taken into consideration as well as the various accessible reports on the subject.

In the course of eight working sessions organised between the months of October 2000 and June 2001 the experts presented a critical analysis and summary of studies published on the various aspects of the theme, according to their field of expertise. The last three sessions were dedicated to summarising and defining the main conclusions and recommendations.

Summary

Cannabis is the most widely used of the illicit drugs. The most recent surveys show that experimentation, as well as more regular cannabis consumption, has been on the increase for about ten years among young people in all the western nations. However, these surveys do not, in France at least, provide any information on the number of young people using cannabis daily, which is the population at risk of presenting with more or less long-term health and social damage in connection with cannabis consumption.

The immediate and deferred pharmacological effects of cannabis are mainly due to Δ9-tetrahydrocannabinol (Δ9-THC), the most abundant of the cannabinoids contained in the plant *Cannabis sativa indica*. However the effects of cannabis consumption on health are also connected with the presence of toxic substances in the smoke, derived from the plant itself or from the tobacco consumed at the same time, particularly in Europe, where this is the most frequent method of use. In addition, the harmful effects of chronic intoxication are also connected with individual susceptibilities.

It is always difficult to find evidence of a causal relationship between the use of a substance and an associated disorder. Prospective studies performed on large populations of users and non-users, with appropriate adjustment of the results for socioeconomic or psychocultural values, are the only ones able to detect subtle and cumulative effects. Studies dealing with heavy consumption, even if the protocols are rigorously controlled, provide information that is often difficult to interpret, because of the frequent use of several substances. In addition, excessive consumption is often associated with another mental illness or with manifest personality disorders, which may be confounding factors in these studies. Excessive consumption could, however, reveal a common vulnerability to an underlying disorder rather than being the factor to trigger the disorder.

Animal studies, even if they cannot substitute for human studies, are entirely complementary and can supply information that clinical studies could never provide. Recent studies indicate that the majority of the effects of Δ9-THC occur through binding to pre-existing receptors in the organism belonging to the endogenous cannabinoid system. This binding activates the signalling pathways leading to modifications in cell activity, in gene expression or in signals to neighbouring cells. Exploration of this endocannabinoid system (receptors and messengers) is quite clearly a very promising sphere for understanding the mechanisms of action of all the cannabinoids.

In 2000 more than half of all 18-year olds in France experimented with cannabis

Studies of the prevalence of cannabis consumption have been performed in the European countries, in North America, in Australia and in New Zealand. With rare exceptions, they deal with the consumption of psychoactive drugs as a whole, such as tobacco, alcohol, cannabis and other substances, and not with cannabis consumption alone.

In France, the proportion of young people aged 20 to 25 who have used cannabis at least once (prevalence of experimentation or lifetime prevalence of consumption) is 57 % in men

and 31 % in women, according to the Baromètre santé (Health Barometer) 2000[1], the most recent study of this subject carried out by the CFES (Comité français d'éducation pour la santé, French Committee for Health Education). The ESCAPAD[2] survey carried out in 2000 by the OFDT (Observatoire français des drogues and des toxicomanies, French observatory on drugs and drugs dependency) on a sample of 13,957 young girls and boys aged from 17 to 19 years gives the following figures for experimentation: at the age of 17: 41 % of girls and 50 % of boys report that they have already smoked cannabis at least once. For boys aged 18 and 19 years these figures are 55 % and 60 % respectively.

In the European survey ESPAD[3](European School Survey Project on Alcohol and Other Drugs) conducted in 1999, 35 % of school students aged 15 and 16 had used cannabis in their lifetimes, which puts France, along with Great Britain and the Czech Republic, at the top of the list of European countries for cannabis experimentation.

It is from 15 years onwards especially that young people experiment with cannabis. Between 12 and 14 years 3.6 % of girls and boys are involved with experimentation, as opposed to 38 % of boys and 30 % of girls in the 15 to 19 year age range (CFES Health Barometer, 2000). As in the Anglo-Saxon countries, the most recent French data seem to show negligible differences between girls and boys in terms of experimentation.

Table I: Proportion of young people aged 14 to 19 years who report using cannabis in their lifetime, by age and gender (data from the ESPAD survey, Choquet et al., 2001)

	Proportion (%)		
	14-15 years	16-17 years	18-19 years
Boys	20.0	42.0	59.0
Girls	13.0	34.0	45.0
Boy:girl ratio	1.5	1.2	1.3

After the age of 30-35 years, the proportion of persons who report that they have used cannabis at least once reduces very rapidly. The main reason for this is the lower exposure of these older generations, found in the majority of European or Anglo-Saxon studies. Prevalence could also vary according to zone of residence, urban or rural. Thus the prevalence of experimentation in Finland is around 20 % in the adult population of Helsinki, but less than 3 % in rural zones.

[1]Survey carried out by telephone interview after random selection from a list of subscribers.

[2]"Health and consumption" survey by anonymous self-questionnaire during the registration day for a defence training course.

[3]Survey by anonymous self-questionnaire on a national sample in schools.

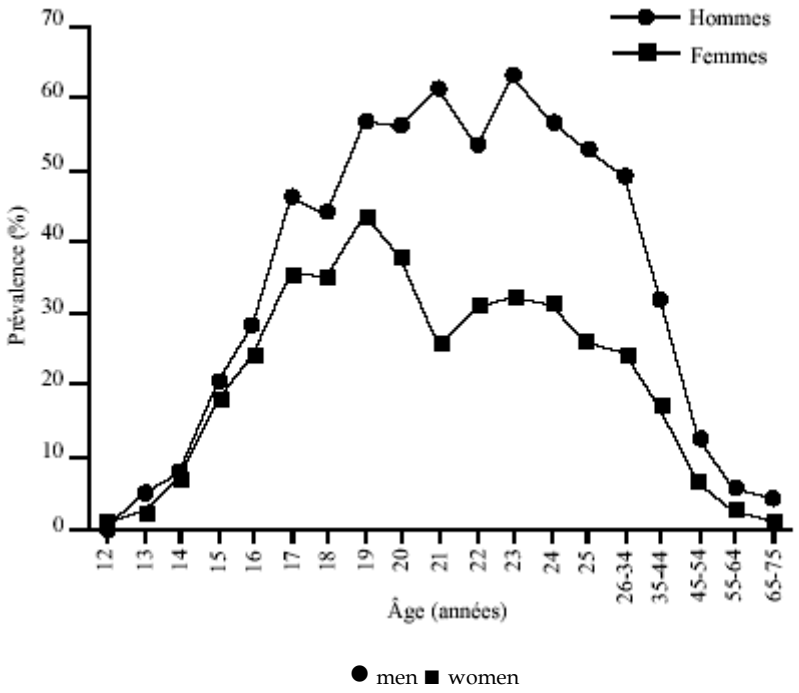

Figure 1: Prevalence-life (%) of cannabis use in the general population, by age and gender (data from the CFES Health Barometer, 2000)

During 2000, in France, about 15 % of 18-year old boys used cannabis more than 40 times

In France, 10.7 % of 15-year olds and 30.8 % of 19-year olds have used cannabis at least once during the past 12 months, according to the CFES Young People's Health Barometer 97-98. The majority of studies performed in the general adult population report a reduction in the prevalence of consumption during the past twelve months after the age of 30 years (12 % prevalence between 26-34 years in men). As in the case of experimentation, this reduction originates in the lower exposure of the older generations.

In France, the prevalence of "repeated" cannabis consumption (10 times or more) during the past year (ESPAD survey) increases from 2 % at 14 years to 29 % at 18 years in boys, and from 1 % to 14 % in girls.

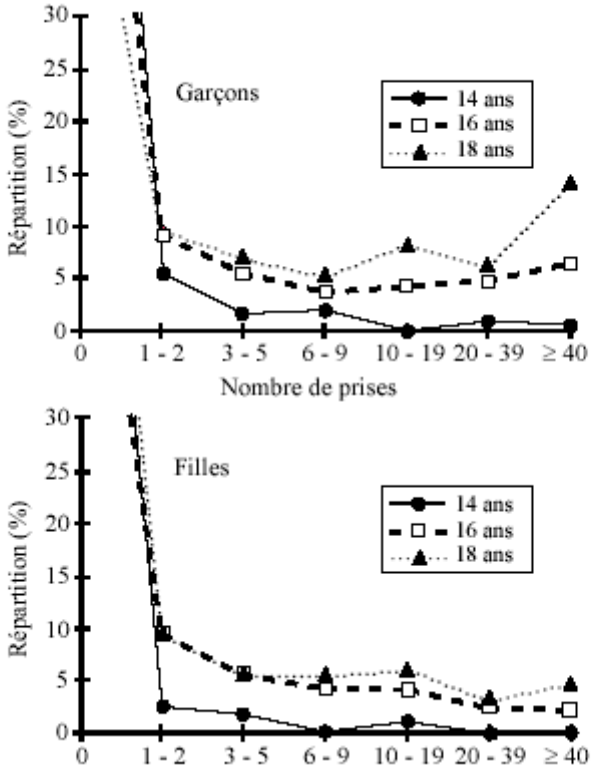

Figure 2: Breakdown (%) of school children according to number of cannabis uses during the past twelve months, by gender and age (data from ESPAD survey, Choquet et al., 2001)

According to the ESCAPAD survey, 12.6 % of 17-year old girls and 23.8 % of boys of the same age used cannabis 10 times during the past year. The figures are 28.5 % and 33.7 % respectively for boys aged 18 and 19 years. The prevalence of cannabis use at 40 times or more in the past year is 18.2 % and 22.9 % respectively in boys aged 18 and 19 years. Based as it was on reported frequency of use, the ESCAPAD survey enabled a typology of cannabis consumption to be constructed ranging from abstainers (40 %) to heavy users who reported at least 20 uses per month (16 %) in boys aged 19.

The surveys conducted in France show that the prevalence of consumption during the past twelve months is higher overall in boys than in girls. This difference is noteworthy in particular for the most frequent users. Thus, according to the ESCAPAD survey (2000), boys aged 17 are almost twice as likely as girls of the same age to report a consumption higher than 10 times in the past year, and almost three times as likely to have used cannabis 40 times and more. With regard to repeated use, these differences in consumption between girls and boys persist in the Anglo-Saxon countries as well.

Significant local variations exist in cannabis consumption. In France, a CFES study shows a significantly greater prevalence of consumption during the last twelve years in Île-de-France than in the rest of France. In the same way, prevalence has been observed to double in school children aged 15 to 16 years in the various regions of Great Britain. Several European studies also show that prevalence during the past year can vary by three times as much according to whether it is a rural, urban or periurban zone that is involved or between different parts of the same town.

The prevalence of consumption in adolescents has risen during the last ten years in France as well as in other western countries.

All the European studies show a significant growth in cannabis consumption during the sixties, which becomes more pronounced during the seventies, while consumption stabilises in the eighties. In the nineties a revival in consumption is noted in all the developed countries, at levels greater than those observed in the ten years that make up the seventies. It is young people in particular who are involved, regardless of the frequency of consumption, whether experimental, during the past twelve months or repeated at least 10 times during the past year.

In Europe, the lower the country's initial consumption, the greater the increase in consumption in recent years. So, experimentation with cannabis in young people aged 15-16 years in Finland doubled between 1995 and 1999, increasing from 5 % to 10 %. In the same way, in France, the prevalence of experimentation in young people aged 15-16 years has risen sharply, increasing from 12 % to 35 % between 1993 and 1999.

Table II: Changes in prevalence-life of cannabis consumption in young people aged 15 to 16 years in different European countries (data from the ESPAD survey 1995, 1999)

Country	Prevalence (%)			
Sweden	1995	6	1999	8
Denmark	1995	17	1999	24
Finland	1995	5	1999	10
Norway	1995	6	1999	12
Great Britain	1995	41	1999	35
Ireland	1995	37	1999	32
France*	1993	12	1999	35
Portugal	1995	7	1999	8
Italy	1995	19	1999	25
Czech Republic	1995	22	1999	35
Poland	1995	8	1999	14
Ukraine	1995	14	1999	20
Hungary	1995	4	1999	11

* Choquet and Ledoux, 1994.

A similar rise in consumption in young people is also reported in other countries such as the United States, Canada, Australia and New Zealand. In Great Britain, a country with a high consumption, as in Italy, the prevalence of consumption seems to have stabilised for some years.

Collecting data on cannabis consumption during the past twelve months enables current data to be compared with those from surveys conducted previously, and changing trends in the prevalence of consumption to be evaluated. In France, according to surveys by the CFES Health Barometer in 1992, 1997-1998 and 2000, consumption rose during the last twelve months, increasing from 5 % to 17 %, then to 26 % respectively in 18-year olds. In adults aged above 30 years, however, the prevalence of consumption during the last twelve months does not appear to have risen noticeably in the last ten years.

The results of the ESPAD European survey in relation to France show that the increase in prevalence of consumption also involves repeated use. Thus, between 1993 and 1999, consumption 10 times or more a year rose by 11 % to 29 % in 18-year old boys, and by 3 % to 14 % in girls of the same age. These supranational trends appear to occur independently of local variations in consumption and of any legislation that has been passed.

The same increase has also been confirmed indirectly, in France as in other European countries, by a group of official figures reporting a very significant growth in the quantities of cannabis seized and in the number of people questioned in relation to cannabis use and use and resale during the last ten years. In France, the latter increased from 4,954 questioned by the police in 1980 to 20,094 in 1990 and to 78,804 in 1999. In the same way the quantity of cannabis seized by OCRTIS (Office central de répression du trafic illicite des stupéfiants, Central office for the Prevention of Illegal Traffic in Narcotics) increased from 33 tons in 1990 to 67 tons in 1999.

The epidemiological data on abuse and dependency are still incomplete

In the fourth edition of the Diagnostic and Statistical Manual (DSM-IV) of the American Psychiatric Association, cannabis dependency is described as compulsive use unaccompanied in general by a physiological dependency. At the same time, tolerance to most of the effects of cannabis has been reported in chronic users, and a withdrawal syndrome described in certain studies.

Several extensive surveys have evaluated the prevalence of cannabis abuse and dependency using a questionnaire drafted in accordance with the DSM-IV diagnostic criteria. These questionnaires, used in the context of population surveys, do not enable diagnosis, but do establish the probability of the subject abusing or being dependent on cannabis when he or she presents with several of the indicators required by DSM-IV. The variables "frequency" and "quantity consumed" are considered equally important.

In the United States, the "Epidemiologic Catchment Area" (ECA), the "National Comorbidity Survey" (NCS), the "National Longitudinal Alcohol Epidemiologic Survey" (NLAES) and the National Household Survey on Drug Abuse (NHSDA) report that the prevalence of cannabis dependency is estimated to be less than 5 % in the general population, and almost 10 % in users. According to these surveys, the prevalence of dependency (lifetime or over the past twelve months) is greater in users aged 15-24 years (15.3 %) than in other age ranges. According to NHSDA, the risk of dependency is twice as high for adolescent users compared with adult users. The highest dependency levels are found, regardless of age and gender, for daily or almost daily use.

In Australia, a study performed on a representative sample of the adult population enabled the proportion of subjects presenting with cannabis dependency according to DSM-IV criteria in the last twelve months to be estimated at 1.5 %. In the sub-group of users who had taken cannabis at least 5 times in the past year, prevalence increases to 21 %. As in the American surveys, it was easier to recruit dependent subjects from those aged from 18-24.

Cannabis consumption was studied in a longitudinal study of a birth cohort of 1265 children born in mid-1977 in an urban region of New Zealand (Christchurch Health and Development Study). At the age of 21 years, 69 % of young people had used cannabis and about 9 % presented with dependency criteria, according to DSM-IV.

A team attempted to correlate the extent of consumption of various psychoactive drugs with the severity of the dependency syndrome engendered. Whatever the substance tested, an elevated consumption involves a higher risk of presenting with dependency criteria (according to DSM-IV). This connection is less obvious for cannabis. Forty per cent of subjects, who had used cannabis more than 6 times, met dependency criteria (in comparison, the equivalent figure for tobacco is 87 %). In two cases out of three, cannabis dependency is moderate or low.

Certain studies report the existence of a cannabis withdrawal syndrome, which may include agitation, sleep disturbance, irritability, nausea, gastrointestinal disorders as well as mild electroencephalic abnormalities. According to the authors, the mildness of this syndrome could in part be explained by the active principle of cannabis, Δ9-tetrahydrocannabinol (Δ9-THC), remaining in the organism for up to three weeks following the last use, a persistence connected with its elimination kinetics and its tissue release. According to a data analysis in the Collaborative Study of the Genetics of Alcoholism (COGA), a withdrawal syndrome would involve 16 % of frequent cannabis users, in particular those who have used the drug almost every day for at least seventy months. This is equivalent to about 5 % to 6 % of the sample studied.

Tobacco, alcohol and cannabis share the same social determinants for initiation of use

There are many determinants for the use of psychoactive substances. This applies equally, of course, to cannabis. Several factors appear to be decisive for the use of both alcohol and tobacco as well as for cannabis, these three drugs often being associated. Protective factors conflict with risk factors. The more protective factors a person has the less likely he is to use psychoactive substances. It is the cumulation of several factors that produces use or abuse.

Combinations of drugs obscure attempts to detect factors that contribute to consumption, which could be specific to cannabis. So, for example, if there is a close association between alcohol and cannabis consumption, and an even closer one between tobacco and cannabis, is the latter only because of their similar mode of consumption, in France as well as in other European countries, where cannabis is almost exclusively consumed in inhaled form and combined with tobacco.

It is probable that experimentation with alcohol, cannabis or tobacco can be explained by use of a single model. In adolescence the model is relatively clear-cut. It is possible that consistent changes to the model occur from adulthood onwards. The fact that studies on cannabis users from older age groups are relatively rare means that the part played by factors of recognised importance in adolescence cannot be confirmed. This model brings three factors into play, all of which have a role in initiating use: family, school and peers influence (friends).

The influence of family background can be expressed by the social model represented by the parents and the quality of their relationship with their children. Children are offered two parental models: one is the use of psychoactive drugs (alcohol, cannabis or tobacco), the other abstinence or regulated consumption. According to the quality of the parent-child relationship, children will adopt either certain consumption behaviours or relative abstinence by distancing themselves from the model their parents offer or imitating it. So parental consumption of psychoactive drugs is a significant factor in inducing cannabis consumption in children. But the fact that the parents do not use psychoactive drugs does not systematically result in abstinence in their children.

School is another important factor influencing the transmission of values to children. A successful adaptation to the school environment, corresponding in part to the adoption of recognised social norms, may influence behaviour in relation to cannabis. The better-adjusted young people are to school (measured by their attitudes to school and teachers and their educational achievement), the less likely they are to have relationships with peers who are using psychoactive substances. Dropping out of education, poor examination results and a poor attachment to school could result in at least an initiation to cannabis.

An other influence will, from a certain age, disturb the family model;, that influence comes from the child's peer group, as cannabis initiation is very frequently a collective act. Peers who are already users, particularly those who are very close to the children, are likely to influence them. Obviously, the greater the presence of cannabis among those close to the child, the higher the risk of use. No single influence completely overrides another at any given time and the ascendancy of one party, whether parents or friends, does not imply rejection of others. What is actually happening here is that the child challenges the values transmitted by his parents in the context of the relationships he is developing with his peer group. This challenge takes place at the point when the child takes some distance from his family and moves closer to his friends of the same age. Young people gradually make their own selection from their family values and from those of their peers, to form their own reference system. This process is clear in adolescents and relates to the theory of at-risk behaviours, which sets the transition from the family cocoon and acquisition of autonomy the focus of explanations of cannabis consumption among young people.

Within this context, if initiation to cannabis were not considered deviant, it could be described as a marker of the acquisition of autonomy. This is not to say that initiation to cannabis use corresponds to a "normal" developmental stage for young people, but simply to observe that it is one of the markers, among others, of young people distancing themselves from their family. After initiation, regular use of cannabis becomes an established response to certain difficult situations, without it being possible to infer a causal connection. Situations involving psychological distress (depression, anxiety, interpersonal difficulties and obsession) and stress facilitate cannabis use, which is then taken as a self-prescribed anxiolytic. In the same way, adolescents reported to be deficient in certain abilities seem more likely to become involved in alcohol or cannabis use and then to increase their consumption.

Sometimes use extends beyond adolescence. However, the greater the extent to which young people assume conventional social roles, especially through marriage or the arrival of children, the more likely it is that they will stop using cannabis. As regards adult users, two categories can be distinguished. The first comprises users whose social integration is "normal", whose consumption poses no apparent problems and the second, users who are less well integrated and whose level of use is higher. It is, of course, impossible to conclude that cannabis consumption is the root cause of less successful social integration. Even if it appears that excessive use may limit the assumption of socially recognised roles, it may equally well be true that unfavourable social conditions increase use, as a means of facing up to these conditions.

Different phases of consumption may give way to others over time. Phases of heavy consumption, self-regulated consumption, stopping or excessive cannabis use may occur in succession, with the result that people follow very different pathways. Changes in times of use may be observed. The person who smokes in the evening only will start smoking in the morning and abstain in the evening. The person who used to smoke at weekends only will start smoking during the week as well. These variations are associated with the different social roles that are taken on in connection with work or family life. Finally, studies of the pathways taken by cannabis users show that stopping cannabis use applies to the great majority of adults after the age of 30-35.

Individual vulnerability factors are associated with cannabis abuse

In France, the Young People's Health Barometer survey 1997-1998 reports that 5.5 % of young French people aged from 15 to 19 years who experiment with cannabis have also used

another psychoactive substance such as cocaine, heroin, crack, amphetamines or hallucinogenic substances. Inversely, it appears that consumption of these substances is almost always preceded by, or associated with, the use of cannabis, tobacco and alcohol. Only 0.5 % of those who have not experimented with cannabis have used one of these other psychoactive substances. The same trend is found if daily tobacco smokers are considered. 3.7 % of the latter have used another psychoactive substance as opposed to the 0.3 % who do not smoke daily. 3.5 % of young people who have already been experienced alcohol intoxication use another psychoactive drug, as opposed to the 1 % of young people, who have never been intoxicated. A recent study of 11-16 year-olds suggests, moreover, that alcohol consumption could be a gateway to the use of cannabis. 11.4 % of young polyusers[4] have used another psychoactive substance, as opposed to 0.6 % of non-polyusers. Overall these data indicate that the proportion of tobacco, alcohol or cannabis users, who become involved in the consumption of other psychoactive substances, is small.

The risk factors for consumption, shared by many types of drug (alcohol, tobacco or cannabis), may be intra- or interpersonal. Adolescence itself is a vulnerability factor. The adolescent needs to affirm his originality, uniqueness and independence, and in doing so to mark himself out from his family and the value systems that have shaped him hitherto. But important individual differences mark the development to adolescence. It is possible to make distinctions between adolescents using cannabis at any given time on their journey by the extent of their cannabis use, whether occasional or excessive and harmful. Vulnerability factors, shared by different subjects, in relation to the use of psychoactive substances have been sought upstream of excessive consumption.

It has been shown that the first-degree relatives of subjects presenting with an addictive disorder are at a higher risk of having a disorder themselves connected with substance abuse. Twin studies show the presence of genetic factors, along with environmental, familial and non-familial factors, at the root of a vulnerability to both cannabis and alcohol. The impact of the genetic factors increases with the extent of consumption. The genetic factors common to a vulnerability to different substances are probably the same as those underlying addictive behaviours along with personality traits which make access to substances more likely (impulsivity, sensation-seeking, antisocial personality disorder). Research into specific genetic factors for vulnerability to cannabis abuse or dependency, as well as to its subjective effects, is focussed on the cannabis receptors and the enzymes involved in endocannabinoid metabolism.

A correlation has been found between the existence of early psychological or mental disorders in preadolescents and repeated cannabis consumption. Very early tobacco consumption and a behaviour disorder may constitute one of the predictive factors for excessive cannabis consumption. Certain studies report that initiation to cannabis, when early, is most often found to be associated with the presence of a behaviour disorder in girls.

Patients presenting with certain mental disorders are more likely to be excessive cannabis users

Cannabis abuse or dependency is diagnosed in 4.0 % to 19.6 % of cases in clinical populations of patients presenting affective disorders (major depressive syndromes and unipolar disorders). In one third of cases the diagnosis of abuse precedes depressive symptomatology. Other results suggest that the age of onset of dependency corresponds to

[4]The consumption of alcohol several times a week and/or more than ten cigarettes per day and/or cannabis more than ten times during the past year.

the age of onset of the major depressive syndrome.

Table III: Prevalence of cannabis abuse or dependency in clinical psychiatric populations

Disorders	Prevalence (%)
Affective disorders	4.0-19.6
Bipolar disorders	13.4-64.0
Suicidal behaviours	16.2-31.0

Different studies performed in the clinical population of patients suffering from bipolar disorders show that 13.4 % to 64.0 % of patients present with cannabis abuse. For some of these patients cannabis is a way of reducing depressive and, more particularly, manic signs. Abuse occurs then as a treatment for bipolar disorder.

Studies find significantly more patients who abuse psychoactive substances, including cannabis, among the clinical populations of patients who have made a suicide attempt, than among the general population, where the prevalence for cannabis abuse varies from 16.2 % to 31 % according to studies. The prevalence of suicide attempts is also significantly higher in the cannabis abuse patient group than in the general population (25.8 % vs 6.5 %), especially when an associated psychopathology is present. This high prevalence of suicide attempts is often associated with the existence of more significant depressive symptoms. According to several studies, cannabis abuse can be considered an independent predictor of suicide attempts both in the general and clinical population. The risk is further increased when abuse involves several substances rather than cannabis alone. Studies, notably French ones, suggest that young polyusers of tobacco, alcohol and cannabis present more risk behaviours such as acts of violence either suffered or perpetrated and suicidal thoughts. Polyusers would thus be about five times more likely than non-polyusers to report that they have already attempted to take their own life.

There has long been an association between behaviour disorders in children and antisocial personality disorder in adults and the diagnosis of disorders connected with the illicit substance use. This association probably originates in the fact that substance abuse is one of the diagnostic criteria for the diagnosis of an antisocial personality. It is admitted now that two thirds of patients presenting a personality disorder, in particular of the borderline type, are also diagnosed as suffering from disorders connected with the use of psychoactive substances according to DSM-III-R. In various studies performed in the clinical population of patients presenting with cannabis abuse, the personality disorders most frequently found are the borderline type and, at a lower level, the antisocial type.

The consumption of psychoactive substances does appear to be an aggravating factor for several mental disorders. In certain studies performed on female bulimic patients, the cannabis user group presents, over the whole of their lifetime, with more affective disorders and anxiety disorders than bulimic non-users.

The effect of cannabis consumption on sexual behaviour (performance, desire, sexual pleasure) has been explored in many studies. Independently of reports that cannabis plays the role of an aphrodisiac, study results converge and find an increase in pleasure in men and in desire in women, in combination with loss of inhibitions. The number of sexual partners appears to be significantly increased, and "at risk" sexual behaviours (non-use of condoms) have been reported. In a study performed on a population of sexual aggressors, cannabis was the second most likely substance, after alcohol, to be detected in relation to the loss of behavioural inhibition provoked by these substances.

Do common factors explain the co-occurrence of schizophrenia and cannabis abuse?

The relationships between cannabis and schizophrenic disorders have been the subject of much debate and remain complex. This is likely to be a problem that has been underestimated by clinicians. According to ECA data, the prevalence of schizophrenic disorders in subjects who abuse or are dependent on cannabis is 6 %, although it is about 1 % in the general population. In addition, according to the relevant studies, 13 % to 42 % of schizophrenics have been abusers of, or dependent on, cannabis at some time in their life. 8 % to 22 % have been so in the six months preceding the interview. A survey conducted in France reports that 36 % of hospitalised schizophrenic subjects are, or have been, dependent on cannabis.

In relation to schizophrenia alone, schizophrenia associated with cannabis abuse is characterised by the earlier onset of the disorders, less therapeutic compliance, more frequent recourse to accident and emergency departments and to hospitalisation, greater social exclusion, more marked risks of depression and of transition to acts of suicide, more frequent psychotic relapses and by problems in formulating a request for care. However, less conceptual disorganisation and disorganisation of train of thought and less marked productive and deficit symptoms can be observed.

Treatment of these subjects is marked by problems of management. They are more ready to admit, like their family for that matter, their drug abuse than their schizophrenia. On the other hand, some of them find, in toxic substances, a means of sedation and of controlling their anxiety, despite an aggravation of the disease process and of its social consequences. When treated however, these patients may have a better course.

This association between schizophrenic disorders and cannabis abuse could originate from various situations, either self-medication of a primary schizophrenia in an attempt to relieve the first symptoms of anxiety and anhedonic affect or the primary use of cannabis accompanied by the development of a secondary schizophrenic disorder. The second hypothesis of drug-induced psychosis reflects a vulnerability to schizophrenia, which cannabis use reveals or augments and raises the question of disorders, which would not be decompensated without a trigger or activating factor. There are grounds for proposing that a dysfunction of the endocannabinoid system plays a role in the pathophysiology of schizophrenia, which cannabis consumption could aggravate. This specific association between schizophrenia and cannabis abuse could indicate the presence of a vulnerability common to these two disorders, of genetic, environmental, psychological or social origin.

The pharmacological effects of cannabis mainly originate from Δ9-THC

The chemical composition of *Cannabis sativa indica* (Indian hemp) is highly complex. Among more than sixty cannabinoids identified to date in the plant, the substances which are principally responsible for the pharmacological effects in humans are Δ^9-tetrahydrocannabinol (Δ^9-THC) and, to a lesser degree, Δ^8-tetrahydrocannabinol and Δ^9-tetrahydrocannabinolic acid (transformed into Δ^9-THC during combustion). A pronounced variation in Δ^9-THC concentrations is observed in the herb (mixture of leaves, stems and flower heads) and also in the resin ("hashish") in cannabis-based drugs found in France. Δ^9-THC concentrations of less than 2 % are relatively frequent (18 % of samples). Until 1995, the mean concentration was 5.5 % for the herb and the highest content found in drugs seized was 8.7 %. During the same period, resin samples contained on average 7 % Δ^9-THC, with a

maximum of 10.6 %. Since 1996, although in general the content of the majority of samples has changed little (about 8 % for the herb and 10 % for the resin), cannabis-based samples with a very strong Δ^9-THC concentration have appeared, up to 31 % for the resin and 22 % for the herb. During 2000, 3 % of herb samples and 18 % of resin samples analysed contained more than 15 % Δ^9-THC. New drugs have appeared on the French market since 1998: the "skunk" (variety of cannabis flowers originating from the United States and the Netherlands) and the "pollen" (stamens of male plants) contain even higher Δ^9-THC concentrations.

Attention should be given to toxicity of associated substances originating from the cultivation method (pesticides for example) or preparation method (colorants, paraffin, animal excrement, used motor oil) while few data is reported in the litterature.

Depending on how cannabis is smoked, 15 % to 50 % of the Δ^9-THC present in the smoke is absorbed and passes into the bloodstream after inhalation. Absorption is very rapid. One study showed that maximum blood concentrations are obtained in less than ten minutes and that they are dose-dependent. The products of metabolism of Δ^9-THC are mainly 11-hydroxy-Δ9-tetrahydrocannabinol (11-OH-Δ9-THC), a metabolite with pharmacological effects and 11-nor-9-carboxy-Δ9-tetrahydrocannabinol (the THC-carboxy metabolite, THC-COOH), which has no pharmacological effect.

Table IV: Concentration, time of appearance[1] and duration of detection[2] of the cannabinoids in the blood after consumption of a marijuana cigarette containing 15.8 mg or 33.8 mg of Δ^9-THC (Huestis et al., 1992)

Compound	Maximum concentration (ng/ml)	Time at which peak appears (h)	Duration of detection (h)
Δ9-THC	84.3 (50-129)* 162.2 (76-267)**	0.14 (0.10-0.17) 0.14 (0.08-0.17)	7.3 (3-12) 12.5 (6-27)
11-OH-Δ9-THC	6.7 (3.3-10.4) 7.5 (3.8-16.0)	0.25 (0.15-0.38) 0.20 (0.15-0.25)	4.5 (0.5 4-12) 11.2 (2.2-27)
Δ9-THC-COOH	24.5 (15-54) 54.0 (22-101)	2.43 (0.8-4.0) 1.35 (0.5 4-2.21)	84.0 (48-168) 152.0 (72-168)

1: mean interval between the onset of consumption and the appearance of a concentration peak; 2: mean interval between onset of consumption and the time at which the lowest concentration of the compound is detected (> 0.5 ng/ml); *: cigarette containing 13.8 mg (1.75 %) Δ9-THC; **: cigarette containing 33.8 mg (3.55 %) Δ9-THC.

Δ^9-THC is highly lipophilic and is rapidly distributed in all the lipid-rich tissues, mainly the brain. Tissue binding is responsible for a rapid decrease of Δ^9-THC blood concentrations. The prolonged psychoactive effects, which may persist for as long as 45 to 150 minutes after stopping consumption, result from its pronounced lipophilia, as well as from the part played by the enterohepatic cycle and renal reabsorption.

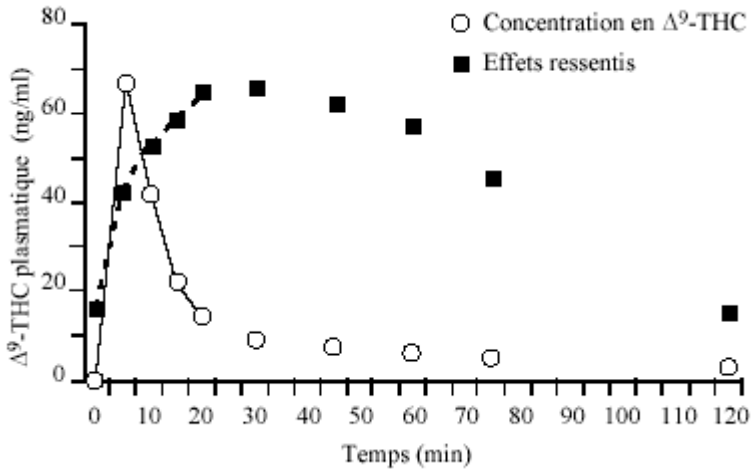

Figure 3: Δ⁹-THC concentrations (open circles) and the physical and psychological effects "experienced" by the subject (filled squares) in relation to time, after smoking a cigarette containing 9 mg Δ⁹-THC (Harder et al.,1997)

The elimination rate of the cannabinoids is highly variable and depends on a number of parameters: dose, regular or occasional use and may be the subject's degree of adiposity. Δ⁹-THC and its metabolites are eliminated by various routes: gastrointestinal, renal and via the sweat. The half-life (time required to eliminate half the dose present in the organism) of Δ⁹-THC is about eight to ten days in adults with normal hepatic function. The fact that elimination is slower than for other psychoactive substances leads to an accumulation of Δ⁹-THC, especially in the brain, in the case of a regular user.

By reason of its pronounced lipophilia Δ⁹-THC passes into the mother's milk and across the placenta. The concentrations detected in the foetal blood are at least equal to those in the mother.

Δ9-THC and its metabolites can be analysed in the urine and blood

As far as the detection of cannabis use is concerned, it is important to make a distinction between the screening methods used for orientation purposes and confirmation procedures and assay techniques. Cannabis use can be detected by immunochemical methods, either by using automated analyzers or by performing rapid tests, which enable results to be obtained in a few minutes. For reasons of sensitivity and specificity, these immunochemical methods are, to date, exclusively reserved for urine and cannot in any case be used for other biological media such as blood. Because false positives are possible (because of cross-reactivities with other substances) every positive result obtained by an immunochemical method must always be confirmed by a specific separation-based method.

As regards urine testing, numerous detection tests are on the market, some of which are sufficiently reliable in terms of specificity and sensitivity. Δ9-THC-COOH (inactive) is the metabolite that is most frequently recovered in the urine. Today the threshold concentration for a positive result is 50 ng/ml. Urine testing enables detection of cannabis consumption, but does not permit judgements to be made about the period that has elapsed from the time cannabis intake and the time the urine was collected.

Saliva could be a good, readily accessible detection medium in which the presence of Δ9-THC reflects recent use (not detectable 2 to 10 hours later). Very low levels of cannabinoids pass into the saliva from the blood. The presence of Δ9-THC in saliva is essentially due to the phenomenon of bucco-dental sequestration on inhalation. Although this environment is potentially of interest, particularly so for the purposes of mass screening, to date no

commercial device exists that is suitable for this biological medium.

Sweat is a very poor environment for testing, as it is exposed to environmental contamination and the presence of Δ9-THC in sweat does not reflect recent use. In addition, to date, there is no reliable commercial device appropriate for the detection of Δ9-THC in sweat.

Confirmation of cannabis consumption requires chromatographic separation procedures. Currently the reference methodology is gas chromatography with mass spectrometry (GC-MS). The blood is unanimously accepted as being the only biological medium appropriate for the purposes of confirmation of cannabis use. Basically only GC-MS analysis of the blood enables active principles and inactive metabolites to be distinguished and a quantitative analysis to be performed in parallel. It also makes possible estimation of the period that has elapsed between the time cannabis was last used and the time the blood sample was taken. This is why GC-MS analysis of blood samples is the only method accepted in every medicolegal context (including accidents on the public highways).

Hair reflects repeated exposures and consequently enables a timetable of exposure to be established. Each centimeter of hair represents approximately one month's growth. An analysis of segments makes characterisation of the consumption profile and course possible. Δ9-THC is the most frequent metabolite to be found in the hair. Only a very low quantity of Δ9-THC-COOH (< 1 %) is present. Analysis of the cannabinoids in hair makes it possible to detect chronic users and to establish a level of use (low, moderate or high), which is impossible with urinalysis. This approach provides a better measure of abstinence than follow-up urine testing. Hair analysis has numerous applications in legal medicine, occupational medicine, traffic medicine and surveillance of doping.

Table V: Main characteristics of the various biological media used to detect cannabis consumption

	Cannabinoids most frequently detected	Maximum detection period	Field	Available methods
Urine	THC-COOH (inactive)	Occasional use: 2 to 7 days Regular consumption: 7 to 21 days	Screening for use	Yes, numerous rapid tests
Saliva	THC (active)	2 to 10 hours	Screening for recent use	No, no rapid tests
Sweat	THC	Very variable	Of little value	No, no rapid tests
Blood	THC 11-OH-THC (active) THC-COOH	2 to 10 hours	Confirmation, identification, assay	Yes, GC-MS
Hair	THC	Infinite	Detection and follow up of regular use	Yes, GC-MS

GC-MS: gas chromatography-mass spectrometry; THC: Δ9-THC.

Few data exist on the correlation between effect and blood concentration, in particular when concentrations of the active metabolite are low. In fact, while the data from the literature enable pharmacological effects (mydriasis, conjuctival injection, behavioural disorders) to be assigned to significant blood concentrations of Δ9-THC (several ng/ml), interpretation of the results becomes very difficult when this concentration is close to or less than 1 ng/ml. To assist with the interpretation of results one study proposed a formula combining Δ9-THC, 11-OH-Δ9-THC and Δ9-THC-COOH concentrations, which results in a "Cannabis influence factor". A value above 10 denotes the presence of pharmacological effects. However, other authors have never validated this study, which was performed in 1996.

Is it dangerous to drive after using cannabis?

Studies performed in the United States and Europe and in Australia have attempted to define the nature and the true extent of the problem of the use of psychoactive substances, including cannabis, when driving a car. Some used the epidemiological approach, and some the experimental approach (simulators, psychomotor tests).

During the nineties cannabinoids appeared in the first rank of illicit psychoactive substances detected during surveys performed among drivers involved or not involved in accidents. The frequency with which cannabis is detected depends on the populations being surveyed. Assessment relies to a great extent on how the samples of drivers tested are selected (whether they are representative or not) and on the means of cannabis detection employed (biological medium, detection of Δ9-THC or of its metabolites, assay techniques).

In surveys of subjects who have been involved in accidents the latter are made to give a blood or urine sample (sometimes both) and cannabis consumption is detected by detection and assay of Δ9-THC in the blood or of Δ9-THC-COOH in the blood or urine. The significance of a positive result for the cannabinoids is not always of unequivocal significance in terms of road safety. The presence of a certain degree of Δ9-THC in the blood testifies to recent cannabis use which could impair the ability to drive, whereas the presence of Δ9-THC-COOH in the blood or in the urine reveals consumption that could sometimes date back to several days or even weeks and have no connection with potential effects on driving behaviour. Given the rapid drop in blood Δ9-THC concentration, the time that has elapsed between the accident and taking the sample has a pronounced effect on the result. Ideally it should be as short as possible. The methodology selected should be taken into account when interpreting the prevalence figures from various surveys. The prevalence of cannabis detection in drivers involved in traffic accidents in France varies from 6.3 % to 16 %, or even 34 %, when requisitions made at the request of the public prosecutor are concerned. These studies are an accurate reflection of how diverse current practice is and consequently of how difficult it is to compare results. In relatively representative samples of drivers involved in accidents in Europe, the estimated proportion of subjects testing positive for cannabis varies in a similar manner, from 5 % to 16 %. The proportion of drivers suspected of driving under the influence of psychoactive substances is, not surprisingly, higher. It depends above all on the selection made by police officers. Finally, in a large number of studies, a substantial proportion of drivers testing positive for cannabis are also positive for alcohol (about 50 % in studies in France). The latter then appears as a significant "confounding" factor in the evaluation of cannabis-associated risk.

It is impossible for ethical reasons to force a driver taken from circulating traffic to give a blood or urine sample. Studies performed in Germany, the Netherlands or in Quebec, which employ, on a large scale, alternative methods for collecting urine and saliva at roadside sites are considered as pilot studies. The proportion of subjects testing positive for cannabis, between 1 % to 5 %, appears lower than that detected when accidents occur. At the same time, these results are inconclusive because of missing data and the high number of motorists who refuse to co-operate.

In order to study the effects of cannabis consumption on driving, researchers subject volunteer drivers (non-users or occasional users) to various batteries of tests (sensory, psychomotor or simulator tests) or observe them in an actual driving situation. Despite various methodological problems - defining the assay procedure, administration of the substance or experimental design - the results show a clear deterioration overall in certain abilities under the influence of cannabis: slowed reaction time, reduced ability to control a path, poor appreciation of time and space, impaired or inappropriate response in an

emergency. However, different authors still judge the extent of the impairment very differently, in particular in the actual situation. Some studies conclude that drivers under the influence of cannabis would "compensate" for the reduction in their abilities by modifying their behaviour. This hypothesis is still controversial. In addition the authors all insist on the individual variability of effects. Negative behavioural changes generally appear to be significant for high doses of cannabis only. The combined use of alcohol and cannabis compared to that of cannabis alone leads to much more significant reductions in performance. This finding remains true in the actual situation, including cases when low or moderate doses of cannabis are combined with low doses of alcohol. As far as any assessment of the validity of these experimental results is concerned, it remains unclear whether all the behavioural aspects, particular those affected in the actual situation, are adequately described in the tests and in the responses measured. In particular, what precisely are the tasks which drivers should be asked to undertake in order to evaluate their failings as accurately as possible?

Despite the assumption that it is dangerous to drive after or while using cannabis, even today it is still impossible to state, in the absence of reliable epidemiological studies, that there is a causal connection between cannabis use and road traffic accidents. The first difficulty epidemiologists are confronted to is establishing a control group. The other major difficulty is the absence of a synchronous relationship between the presence of cannabis (blood or urine) and its effects on behaviour. Δ9-THC level may actually be almost zero and yet the harmful effect may last, or conversely, the metabolites may be detected well after all psychological effect or deterioration in abilities has disappeared. It is difficult, then, to classify subjects as those who are "exposed to the cannabis risk" and those who are not. Some teams have nevertheless attempted to establish a cannabis-accidents relationship by using an approach founded on an analysis of responsibility. A relative overrepresentation index of cannabis users among those responsible for accidents is employed instead of an indicator of increased risk. The distinction between those responsible and not responsible should itself be made with caution once it has to be strictly independent of cannabis consumption and of the variables correlated with it (alcohol in particular). Relevant publications take into account these various biases as far as possible and confirm the importance of alcohol risk, but fail overall to demonstrate any independent effect of cannabis on responsibility for accidental injury or death. Their results do suggest, however, that alcohol and cannabis combined represents a risk factor greater than that of alcohol alone. They also tend to show that the risk of responsibility increases at high Δ9-THC concentrations.

Overall, the results of different types of study do agree that the degree to which cannabis makes driving dangerous could depend on its modes of consumption, whether in a substantial quantity (elevated blood Δ9-THC concentrations) or mixed with alcohol. Beyond the remaining questions about the role of cannabis as a risk factor for accidents at the population level, substantial progress has been made in the observation system itself, with the development of biological media, appropriate thresholds and devices suitable for roadside use. Saliva tests are promising in this regard. This progress is sustained by the desire both to acquire knowledge and to take action in the sphere of psychoactive substances and traffic on the European level. While a relationship may have been established between existing measures relating to alcohol and measures developing for other psychoactive substances, the scientific foundation, in the case of cannabis, still seems incomplete.

Cannabis consumption has immediate or short-term effects

The acute somatic effects of cannabis consumption are mainly due to the effects of Δ9-tetrahydrocannabinol (Δ9-THC).

There has never been any reported case of death in humans after isolated acute intoxication with cannabis. The initial determination of lethal doses in rats has not been reproduced in any of the most recent studies, all of which used substantial doses of Δ9-THC. However, ingestion of large quantities of cannabis, such as a child taking it accidentally, may involve disorders of consciousness and even coma. Finally there have been reports of vomiting or diarrhoea when high doses of cannabis are taken.

The acute somatic signs appearing after cannabis consumption are often minor and inconsistently reported. The cardiovascular manifestations vary in relation to Δ9-THC concentration. Heart rate and cardiac output normally increase and peripheral vasodilatation explains while orthostatic hypotension or headaches occur. The bronchopulmonary effects are similar to those of tobacco. They are manifested by a cough signalling bronchial irritation. This effect is connected with the direct action of Δ9-THC and with the potential mucosal irritant effect exerted by the products of combustion (associated tars). The transient bronchodilatory effect of Δ9-THC does not prevent the bronchial inflammation that is a consequence of smoking cannabis. Δ9-THC leads to mild respiratory depression, for which no clinical effects have been demonstrated. Other effects have been described consisting of ocular effects ("red eyes" because of vasodilatation and conjunctival irritation), gastrointestinal effects (buccal dryness because of a reduction in salivary secretion, reduction of intestinal motility) and urinary effects (urinary retention). Most of the acute somatic effects of cannabis use are attenuated in chronic use, because pharmacodynamic tolerance develops.

The acute effects of cannabis on cognitive and intellectual function have been investigated in the laboratory in volunteers subjected to a standard test battery intended to measure their memory, intelligence, sustained attention, information processing and problem solving ability, their ability to learn or abstraction ability. The studies demonstrated short-term amnesiac effects (working memory). Cannabis use has an adverse effect on subjects' ability to recall words, images, stories or sounds presented while taking the drug, immediately or several minutes after their presentation. The performance of volunteers in tests other than assessments of memory is either unchanged or only slightly changed according to the study in question. Positron emission tomography enables modifications in the blood flow in different regions of the brain to be detected in volunteers subjected to auditory tests before and after using cannabis.

The effects observed in users are similar to those distinguished in the laboratory. Doses that induce drowsiness, moderate euphoria and feelings of well being are associated with deterioration in temporal perception, short-term memory disorders and an inability to divide attention among simultaneous tasks. When cannabis use is higher, language disorders and impaired motor co-ordination may appear, as well as dysphoria. Reaction time is also increased. At high doses some of these cognitive changes may last up to 24 hours. The deterioration in functional ability may affect the performance of psychomotor tasks and should be taken into account, especially by subjects whose work involves any risk to the safety of others. Finally disorders of memory and learning ability may also have effects on schoolwork and social adaptation. This is the most problematic deterioration, because it is frequently encountered in connection with repeated cannabis use.

Elevated cannabis consumption can cause psychosis

The concept of cannabis psychosis was first proposed on the basis of case studies, then in

some comparative studies of schizophrenic disorders. These studies are rendered problematic by the coincidence between the peak age range for cannabis use and that of the onset of psychotic disorders on the one hand, and by the diagnostic problems of differentiating between acute delirious outbursts and the paranoid outbursts of schizophrenia on the other. Furthermore, studies conducted in countries where consumption is heavy (India, Southern Africa, and the West Indies) employ methodologies that are often questionable, with insufficient rigour in diagnosis. Finally the illegal status of cannabis means that the prevalence of consumption is underestimated.

Some case studies of adult subjects, who are well adjusted socially and affectively, make it possible to state unequivocally that cannabis psychosis exists. The psychotic disorders induced by cannabis are recognised in international classifications of mental illness (DSM-IV, CIM 10). They occur at the same time as cannabis intoxication or in the month following the stopping of intoxication. Their incidence is low in relation to the number of user subjects (it involves about 0.1 % of user subjects in Sweden in one study). In certain countries with high consumption, however, cannabis psychosis is one of the most frequent reasons for admission to psychiatric hospital. It involves by definition brief psychotic disorders, lasting from eight days to two months, or three months at the very most. The semiology of cannabis psychosis is close to that of acute delirious outbursts, with more heteroaggressive behavioural disorders connected with psychomotor disinhibition and a far greater frequency of non-verbal hallucinations especially visual ones and of "deja vue" feelings or depersonalisation. The premorbid personality does not appear to present disorders with a psychotic course. Onset is sudden and resolution on neuroleptic chemotherapy effective. These clinical pictures are preceded by a recent increase in the use of toxic substances and relapse more readily when the substance is used again.

This induced psychosis is reminiscent of other clinical pictures connected with cannabis use, which are suggestive of disorders with a psychotic course, but are less manifest. Habitual cannabis intoxication is characterised by an introspective euphoria. At high doses (300 to 500 µg/kg, that is about ten standard joints), intoxication is a transient psychotic experience with excitation and dissociation of thought, fixed ideas and delirious convictions, irresistible impulses, illusions and hallucinations. According to how pronounced these symptoms are, the clinical picture tends to be excitatory, delirious or pseudodementia in appearance. Severe amotivational syndromes, with the appearance of pseudodementia, have been reported in heavy users, in particular in countries where consumption is high. Although more pronounced, these syndromes are reminiscent of the lack of motivation observed in regular consumers. States of transient or continuous depersonalisation or of atypical anguish may be observed. Hallucinosis may occur (in particular in subjects with a multiple substance abuse on methadone treatment) without delirium, and may be acute or almost continuous. Cannabis psychosis regresses rapidly under neuroleptic agents. As is the case for all toxic substances, states of mental confusion can be observed. Finally, the clinical pictures where euphoria and hallucinations, reoccur spontaneously in the three months following cannabis use, currently known as flash-backs, in which the subject relives his experiences on the toxic substance, are very rare.

Repeated cannabis use may have longer-term effects

The somatic effects occurring after chronic cannabis use may be due not only to Δ9-tetrahydrocannabinol (Δ9-THC) but also to other substances contained in smoked or ingested drugs (other constituents of the plant, combustion products, products of "blending").

In cases of chronic use the pulmonary toxicity connected with the mode of preparation and consumption of cannabis (its combination with tobacco and also with other substances contained in the drug) manifests as inflammatory reaction, obstructive syndrome and a modification in alveolar permeability. In addition, isolated cases of arteriopathy have been reported, in which Δ9-THC as well as other constituents of cannabis and concomitant tobacco smoking are implicated.

Effects on the endocrine system have also been observed in cases of repeated consumption: a moderate reduction in blood concentrations of testosterone and hypophyseal hormones (luteinizing and follicle stimulating hormone), the clinical consequences of which are still under discussion. In various studies substantial chronic cannabis consumption has been associated with a reduction in spermatozoid production, although there is no current clinical evidence of hypofertility, as well as a reduction in the size of the prostate in men and the presence of anovulatory cycles in women. These disorders are reversible when use is stopped.

Research into the long-term cognitive effects in chronic users is performed using laboratory tests after a short period of abstinence. Interpretation of the results is a delicate matter by reason of the methodological difficulties of matching the subjects. Older studies performed in Jamaica, Greece, Costa Rica or in India have not succeeded in detecting differences between chronic users and non-users. Some more recent studies have reported subtle deficits in heavy users, detected after a brief (24-hour) period of abstinence, which could last up to six weeks. The cognitive effects, when they are observed in heavy users, who are not under the influence of the drug, essentially involve short-term memory (memory tests, sorting cards). A handful of studies using the specialised techniques of encephalography have revealed minor anomalies in the amplitude of certain waves in response to visual or auditory stimuli in chronic cannabis users.

Various studies, either experimental or studies of students or employees, have attempted to evaluate the impact of cannabis consumption on motivation, performance and educational or professional success. The results of these studies remain contradictory at present. Certain clinical case studies have, however, described an amotivational syndrome (reduced commitment to professional or educational activity and also poor ideation and affective indifference) in very heavy users.

Chronic cannabis consumption could increase the risk of certain cancers

Any evaluation of the carcinogenic effect of regular cannabis use must take into account the mode of consumption (whether combined with tobacco or used pure in the form of marijuana) as well as levels of tar and of other carcinogenic substances contained in different inhaled preparations. The quantity of tar in the smoke from a cannabis cigarette (about 50 mg) is higher than in a tobacco cigarette (12 mg). The concentration of carcinogenic substances (benzanthracene or benzopyrene, nitrosamines, aldehydes) is also higher in the tar. Furthermore, the bronchodilatatory effects of Δ9-THC could promote the retention of tar in the upper airways.

When tested in vitro, Δ9-THC is not mutagenic either in the different strains of Salmonella typhimurium tested or in Chinese hamster ovary cells (CHO cells) without metabolic activation by rat liver fraction. No chromosomal aberrations are observed either nor is there micronuclei formation. However, Δ9-THC induces exchanges of sister chromatids under certain conditions. In cell cultures Δ9-THC inhibits the expression of histone genes. In animal studies no increase in cancers was detected after prolonged administration of Δ9-THC (two-

year carcinogenicity study).

The carcinogenicity results are more convincing when tar or cannabis smoke is tested. Mutations similar to those induced by tobacco are observed in tests on bacteria. Malignant transformations appear in animal or human pulmonary cells after in vitro exposure to cannabis smoke. DNA and chromosomal deterioration is detected in human lung explants. Genotoxic cellular effects have been observed in marijuana smokers, (mutations, chromosomal deterioration, sister chromatid exchange), as well as a modification in the immunohistochemical detection of certain biomarkers. Accordingly the increase in the expression of the EGF receptor (Epidermal growth factor) and of Ki-67 (marker of cell proliferation) in the bronchial epithelium of these patients is associated with an increase in cancer risk. In the same way p53 tumour suppresser gene is mutated in certain tobacco and cannabis smokers and coded protein expression is abnormal.

Various studies have been performed on the effects of the consumption of smoked cannabis on the development of lung cancers. The results of a case-control study performed in Tunisia suggest that cannabis consumption is a risk factor for bronchial cancer. In this study all patients aged less than 45 years had used cannabis. On the other hand, no subject who smoked tobacco exclusively had cancer before the age of 45 years. These findings could be explained by the hypothesis that bronchial cancer develops in a shorter period when cannabis consumption is added to that of tobacco.

There have been published cases of upper-airway cancer in cannabis and tobacco smokers since the nineteen eighties, but there have also been cases in some young people who smoke cannabis exclusively. In a North American case control study performed in patients suffering from squamous cell carcinoma of the upper airways, a high prevalence of cannabis consumption is associated with cancer of the larynx and tongue. There appears to be a dose-dependent association between marijuana consumption and the development of squamous cell carcinoma. In a more recent case control study marijuana consumption does not appear to be associated with an increased risk of this type of cancer.

Research into the effects on the unborn baby of exposure in utero should be more rigorous

Clinical and epidemiological studies have evaluated the effects of prenatal consumption of cannabis on the offspring in humans and animals.

Studies performed in children born to mothers who are occasional users show no significant differences in relation to a control group, in weight, size, cranial perimeter and gestational age.

Studies performed in children born to mothers whose cannabis consumption was substantial and regular during pregnancy show that this is associated with a reduction in foetal growth. The reduction in the child's weight is estimated to be between 80 g and 105 g but remains less pronounced than that caused by tobacco use. The reduction in gestational age is estimated to be 0.8 weeks.

In prospective and retrospective studies, which have researched malformations, the frequency of minor physical anomalies in children born to mothers who were regular users is no higher than that expected in children born to non-user mothers.

Behavioural anomalies have been observed in some studies in neonates of mothers who are regular cannabis users: increased trembling, decreased visual response to light stimuli, reduction in the strength of crying, deterioration in sleep and increased impulsivity. These

signs generally regress on the 30th day. One study, however, reports the persistence of a decreased visual response in children aged 4 years exposed in the prenatal period. This anomaly disappears at the age of 5 or 6 years. In the same study no reduction in mental and motor performance or language ability has been found in children aged 1 and 2 years. One recent prospective studie conclude that there is a significant relationship between certain behavioural disorders at the age of 10 years and prenatal exposure to cannabis. However, the postnatal environment could play an important role in the persistence of these behavioural anomalies.

It must be noted that most published epidemiological studies are characterised by little or no information on the extent, duration and weekly exposure time of consumption. They tend to contain no analytical confirmation and, by selecting subjects from underprivileged socioeconomic backgrounds, they provide no information on the postnatal environmental conditions that could influence any assessment of effects.

With regard to the development of cancer in the child exposed via maternal consumption, a case control study reports an increased risk of acute non-lymphoblastic leukaemia in children exposed in the pre or perinatal period. Paternal or maternal smoking, however, was not taken into account in this study, although it is a risk factor for leukaemia in the child. Two other case control studies have explored the relationships between maternal cannabis consumption and cancer risks in the unborn child. One reports an increased risk of astrocytoma in children whose mothers were using cannabis at the time of conception or during pregnancy. Results, however, are at the limit of statistical significance. The other study shows an increased risk of rhabdomyosarcoma in children whose parents were cannabis users in the year preceding the birth of their child. This study shows a strong correlation between cannabis and cocaine use, which makes it impossible to determine the independent effects of these two psychoactive substances on the child's cancer risk.

The results of animal studies of the effects associated with prenatal exposure of rodents and primates to massive doses of cannabis extract are inconsistent. One study describes embryotoxicity but not teratogenicity in mice. Contradictory observations have been reported in rats: the anomalies of the limbs, fingers and neural tube closure found in 57 % of rats exposed in one study have never been reproduced. A reduction in foetal weight as well as skeletal immaturity has been detected in rabbits. Deterioration in behaviour (of relevance to social integration and sexual behaviour) has been observed in rats, especially in males. Animal studies with Δ9-THC itself are equally contradictory. In numerous studies no teratogenic effect has been noted in mice, rats, hamsters or chimpanzees. Oral administration (but not subcutaneous or intravenous) of Δ9-THC at 200 mg/kg, however, on D8, D9 and D10 produced an increase in malformations, in particular of the umbilical hernia, club foot or cleft palate type. This last malformation is found in another study in 50 % of mice exposed to Δ9-THC in utero. Finally in rhesus monkeys, injections of Δ9-THC at a dose of 2.5 mg/kg/d at different stages of gestation have led to abortions in the following days. It is important to emphasise that the doses used in animals are very much higher than the consumption described in humans.

Δ^9-THC induces well-characterised behavioural responses in animals

Administration of Δ9-tetrahydrocannabinol (Δ9-THC) and other cannabinoid agonists produces well-defined behavioural responses in rodents: antinociception (inhibition of the pain induced by a stimulus), hypothermia, hypolocomotion and catalepsy. Pharmacological studies performed with knock-out mice suffering from a deletion of the gene coding for CB1,

one of the cannabinoid receptors, have shown that the CB1 receptors are responsible for these responses, which are obtained, however, after administration of high agonist doses. The motor effects of Δ9-THC and cannabinoid agonist compounds have made it possible to demonstrate the specific role played by the endogenous cannabinoids in the cerebral structures responsible for motricity.

Administration of cannabinoids has significant effects on the memory in various animal species. Agonists reduce learning as well as working memory (comparable to short-term memory). However they have no effect on reference memory, equivalent to long-term memory. The CB1 receptors situated in the hippocampus are selectively involved in this response. The majority of studies shows that modifications to the memory are reversible. Longer-term deterioration in memory has however been observed, but after administration of extreme doses of cannabinoids and in certain models that require complex tasks to be performed. The cannabinoids are also capable of increasing slow and paradoxical sleep via a lipid involved in sleep induction, oleamide. Studies performed in rodent anxiety models show that the effects of cannabis on anxiety are biphasic, anxiolytic at low doses and anxiogenic at higher doses. In the same way, after administration of high doses of Δ9-THC an increase in aggressivity can be observed and after low doses a reduction.

Δ9-THC and all the cannabinoid agonists have antinociceptive effects, observed in several behavioural models of nociception (thermal, mechanical, chemical or neuropathic). Electrophysiological studies have largely confirmed these effects. They are independent of other behavioural responses on the part of the cannabinoids. Supraspinal, spinal and peripheral mechanisms appear to participate in the antinociceptive effects of the cannabinoids. At the supraspinal level the periaqueductal grey substance and the rostral ventromedial medulla play an important role. These two structures are part of a descending inhibitory system responsible for the endogenous control of pain and are also involved in the analgesia induced by opioids. The spinal cord also plays an important in the antinociceptive response of the cannabinoids. The CB1 receptors are involved in a selective fashion in the spinal and supraspinal mechanisms responsible for the antinociceptive responses of the cannabinoids. At the peripheral level the CB1 and CB2 receptors might play a physiological role in the control of pain: a release of different endogenous cannabinoids could thus be observed in pain of inflammatory origin. However, the role of the peripheral cannabinoid receptors in the control of pain has recently been contested. The mechanism of the antinociceptive action of the cannabinoids involves, at least in part, a pathway of intercellular signalling independent of adenylate cyclase. They reduce release of the neurotransmitters responsible for pain transmission, such as substance P or calcitonin-gene related peptide. The mechanism of the antinociceptive action of endogenous cannabinoids could be different from that of exogenous cannabinoids. The mechanisms involved in the antinociceptive responses of cannabinoids and opioids are totally independent, even if interactions between these two systems have been described.

Δ^9-THC induces tolerance and subjective effects in animals

The majority of effects observed in animals have been obtained at cannabinoid doses considerably higher than the quantities used by humans, even in the case of substantial chronic consumption. Thus the quantity of Δ^9-THC incorporated by an individual weighing 70 kg, who smokes one cannabis cigarette containing 15 mg Δ^9-THC, would be as high as 40 µg/kg according to some authors. In comparison, some experimental studies use doses, in the order of 10 to 20 mg/kg, administered at least daily by injection.

Tolerance studies have evaluated animals that have undergone repeated administration of different cannabinoid agonists. Tolerance is observed for all pharmacological responses (antinociception, hypolocomotion, hypothermia, catalepsy, effects on body weight and gastrointestinal motility, cardiovascular responses). The onset of tolerance is generally extremely rapid: a much lower response than that induced by first administration of a cannabinoid agonist is seen as early as the second administration. Tolerance seems to be pharmacodynamic in origin: various studies have found a reduction in CB1 receptors in certain cerebral structures or a desensitisation of these receptors. The different cannabinoid agonists present a cross-tolerance, which is not observed for all effects in the case of anandamide, this latter observation suggesting that onset of tolerance to anandamide involves a different mechanism. The tolerance engendered by chronic administration of Δ9-THC disappears at 7 to 11 days after stopping treatment. It is important, however, to note that the doses of cannabinoid agonists used to engender tolerance in animals are massive, very much higher than the doses taken by humans.

The addictive potential of the cannabinoids, like that of all other psychoactive substances, is investigated in animals by studying their abilities to induce physical dependency and discriminative effects and in particular by research into their reinforcing properties.

Table VI: Evaluation of the addictive potential of a psychoactive substance

Properties	Observations
Induction of a physical dependency	Is there a withdrawal syndrome or not?
Induction of specific subjective effects	Discrimination studies: does the animal recognise the subjective and specific effects of a drug or not?
Reinforcing properties	Direct measurement Self-administration: does the animal self-administer the drug or not?
	Indirect measurement Spatial conditioning (conditioned place preference): does the animal seek out or avoid the place where the substance was administered?
	Self-stimulation: does the animal stimulate the cerebral structures belonging to the reward system or not?

Somatic signs of spontaneous withdrawal are in general not observed after stopping Δ9-THC administration. However, a CB1 receptor antagonist is capable of triggering a physical withdrawal syndrome in animals that have been given chronic treatment at high doses of Δ9-THC. Withdrawal is characterised by the presence of somatic signs associated with problems of motor co-ordination and by the absence of autonomic signs in the rodent. The CB1 receptors are responsible for this state of dependency. The doses of Δ9-THC required to induce this state of physical dependency are, again, extremely high, and not comparable to the doses used by humans. Interactions between cannabinoid and opioid dependency have been described. Thus opioid antagonists are capable of triggering a withdrawal syndrome in cannabinoid-dependent animals. Inversely cannabinoid antagonists can provoke a withdrawal in morphine-dependent animals. Cannabinoid agonists reduce the severity of the withdrawal syndrome to opiates. It appears, however, that different cerebral structures are involved in these phenomena.

Discrimination studies have revealed that cannabinoid agonists induce subjective effects, linked in a selective fashion to the activation of the CB1 receptors. Experimental studies did not, however, succeed in identifying whether this sensation was pleasant or not. The discriminative stimulus induced is fairly specific to cannabinoids. However, cross discrimination exists among the different agonists.

Administration of cannabinoid agonists to animals generally induces aversion in spatial conditioning tests. These effects are not observed after administration of anandamide, an endogenous cannabinoid. Specific conditions for Δ9-THC administration, either an attempt to minimise the consequences of its pharmacokinetic properties or prevention of aversion to initial exposure to the drug, have made it possible to observe a conditioned place preference in rats. The reinforcing properties of the cannabinoids have also been observed in the intracranial self-stimulation test at doses similar to those used to induce a conditioned place preference.

Δ9-THC is not self-administered in naive animals of any species. The pharmacokinetic properties of Δ9-THC appear to play an important role in this observation, since self-administration of a cannabinoid agonist with a half-life shorter than Δ9-THC has been observed in mice. Δ9-THC is self-administered in monkeys who have learnt self-administration behaviour with cocaine. These results have been obtained with doses of Δ9-THC comparable to those used by man (in the order of 2 to 4 μg/kg for each injection in monkeys, less than 5 μg/kg for each inhalation of a cannabis cigarette containing 15 mg of Δ9-THC). It should be noted, however, that the behaviour and even the functional state of the reward system in these animals are likely to be modified in comparison with naive animals.

Biochemical studies have shown that the cannabinoids are capable of increasing dopamine release in the nucleus accumbens, which is associated with the potential reinforcing effects of a psychoactive substance. The cannabinoids are also capable of increasing the activity of the mesolimbic dopaminergic neurons belonging to the reward system, which was proposed as the underlying neurobiological basis responsible for the reinforcing effects of various psychoactive substances that are abused.

On the whole, therefore, animal studies show that cannabinoids induce subjective effects. It is possible to induce tolerance and physical dependency on Δ9-THC providing that massive doses of the drug are used. As far as the reinforcing properties of the cannabinoids are concerned, aversion is generally observed in spatial conditioning tests. However self-administration studies, which are the only ones capable of making a direct evaluation of the addictive potential of a substance, reveal that no naïve animal, regardless of species, self-administers Δ9-THC.

Δ9-THC acts through the intermediary of the endogenous cannabinoid system

The pharmacological effects of the cannabinoids are mediated by an endogenous cannabinoid system composed of neurochemical substances (endogenous ligands) and specific receptors. Two types of receptors have been discovered in the natural state. The CB1 receptors were initially isolated in 1990 from rat cerebral cortex. The CB2 receptors were isolated in 1993 from the promyelocytic leukaemia cell line HL60. CB1 and CB2 are 44 % homologous. The CB1 receptor is mainly expressed in the central and peripheral nervous system both in neurons and glial cells. It is also found in peripheral tissues such as the testicles, uterus, immune system, endothelial and retinal cells, but is expressed at much lower levels there. The CB2 receptor, however, is essentially found in the cells of the immune system, although its messenger is detectable in other tissues. CB1 and CB2 are distributed in a fashion that indicates that these receptors are involved in the central and immunomodulatory effects of the cannabinoids respectively.

The cannabinoid ligands can themselves be classified into several groups :

- the natural exogenous ligands: all the cannabinoids produced by the plant Cannabis sativa indica; more than sixty have been counted of which the most abundant is Δ9-THC;
- the endogenous ligands: the main endocannabinoids characterised are anandamide (arachidonoylethanolamide, AEA) and 2-arachidonoyl-glycerol (2-AG);
- the synthetic exogenous ligands: some of these have been obtained by chemical modification of Δ9-THC. Others are very different and may be much more active and more selective than Δ9-THC. The cannabinoid antagonists belong to this class.

Anandamide and 2-arachidonoyl-glycerol are the only endogenous ligands known to bind to the cannabinoid receptors CB1 and CB2 and mimic the pharmacological and behavioural effects of Δ9-THC. Anandamide display characteristics of a full member of the neurotransmitters. In the brain the highest levels of anandamide correspond to the zones of high CB1 receptor expression, that is to the hippocampus, striatum, cerebellum and cortex. However, anandamide is a partial agonist only of the cannabinoid receptors identified. There are strong arguments for assuming the existence of its own receptor.

The majority of biological effects described for the cannabinoids occurs through G-protein coupling by the cannabinoid receptors involving Gi or Go type proteins (Gi/o). Activation of the cannabinoid receptors acts in essence on three major intracellular signalling pathways: inhibition of adenylate cyclase, activation of the protein kinase pathway (MAP kinases) and effects on the permeability of different ion channels.

The inhibitory effects of activation of these signalling pathways involve adenylate cyclase inhibition, then a reduction in cAMP production (one of the main intracellular second messengers) and thus inhibition of protein kinase A. This signalling pathway is activated via the CB1 receptor. Receptors CB1 and CB2 also activate other signalling systems such as ERK1/2 (extracellular signal-related protein kinase) and JNK (c-Jun N-terminal kinase), the protein kinase Akt and transcription factor NFkB (nuclear factor kappa B). An increase is also noted in production of mediators such as the ceramides. All these transduction pathways are implicated in the control of cell viability or death.

The receptors are coupled, through the Gi/o proteins, to ion channels. Activation of the CB1 receptor involves, independently of adenylate cyclase inhibition, inhibition of the N-type, L-type and Q/P-type voltage-sensitive calcium channels. These calcium channels are involved in controlling the release of various neurotransmitters. By means of Gi/o protein coupling still, activation of the CB1 receptors stimulates the inward rectifying potassium channels. The action of the ion channels is expressed globally by a reduction in the release of neurotransmitters in the nerve terminals, which then leads to an inhibition of neuron excitability.

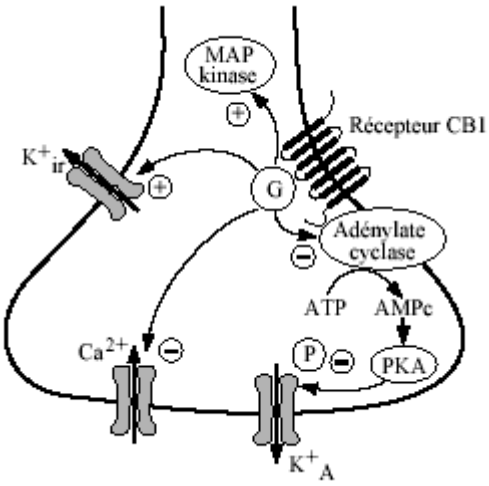

Figure 4: Intracellular signalling of the cannabinoid receptors (Ameri, 1999)

The reduction in intracellular Ca2+ concentration is accompanied by a reduction in neurotransmitter release; in parallel the increase in intracellular K+ concentration is accompanied by a reduction in cellular excitability or the transmission of an action potential.

ATP: adenosine triphosphate; cAMP: cyclic adenosine monophosphate; PKA: protein kinase A; G: G-protein; P: phosphate grouping; MAP: mitogen-activated protein; K+A: A- type potential-sensitive potassium channels; KIR: inward-rectifying potassium channels

In general anandamide reproduces the effects of Δ^9-THC and also possesses its own effects. Thus in the astrocytes (cells playing the role of supporter, supplier and modulator of neurotransmission) it provokes the inhibition of the permeability of intercellular junctions and of the propagation of intercellular calcium signals, as well as the emptying of intracellular calcium stores.

The behavioural effects of the cannabinoids correlate closely with the distribution of receptors in the central nervous system

The CB1 receptors are scattered throughout the central nervous system. Their distribution correlates with the behavioural effects of the cannabinoids on memory, sensory perception and control of movements. Accordingly the highest CB1 receptor densities are observed in the basal nuclei (substantia nigra pars reticulata (SNr) and pars compacta (SNc), globus pallidus, enteropeduncular nuclei, and caudate-putamen) and in the molecular layer of the cerebellum. The pronounced expression of CB1 in these structures fits in perfectly with the inhibitory effects of the cannabinoids on motor performance and co-ordination. The pronounced expression of CB1 in layers I and IV of the cortex and in the hippocampus, where they modulate the elementary forms of synaptic learning, may explain the cannabinoids' reversible but harmful effects on the cognitive functions.

The weak expression of the cannabinoid receptors in the brain stem where the centres of cardiovascular and respiratory control are located, explains the low acute toxicity of the cannabinoids and the fact that no cases of fatal intoxication in man have been reported. The actions of the cannabinoids on the CB1 receptors of the thalamocortical system and spinal cord play a role in sensory disturbances and in their antinociceptive action. The activation of the CB1 receptors present in the structures controlling nociceptive transmission, such as the periaqueductal grey area and the dorsal horn of the spinal cord, as well as in the peripheral terminals themselves (where the presence of CB2 receptors is also observed), plays a role in the substantial antinociceptive effects of the cannabinoids. The CB1 receptors of the

hypothalamus play a role, no doubt, in the mild hypothermia induced by the cannabinoids.

Table VII: Principle CB1 receptor densities in the central nervous system and correlated pharmacological effects

Structures	Density	Physiological results
Cerebral cortex	++	Cognitive effects
Basal nuclei	++	Locomotor effects
Hippocampus	++	Cognitive effects (short-term memory); antiepileptic effects
Thalamus/hypothalamus	++	Endocrine and antinociceptive effects
Periaqueductal grey area	+	Antinociceptive effects
Cerebellum	++	Motor effects (balance)
Brain stem	-	No mortality

++ : high; + : intermediate; - : low or none

As regards the cerebral structures belonging to the endogenous reward system involved among others in the reinforcement of certain types of behaviours (sexual behaviour, taking food, sensation seeking and consumption of psychoactive substances), it is possible to observe a moderate CB1 density in the nucleus accumbens, none in the dopaminergic cells of the ventral tegmental area and a high density in the pre-frontal cortex and in the fibres of cortical origin projecting towards the nucleus accumbens. These data suggest the presence of CB1 receptors on the afferent terminals of these structures. Within the corticomesolimbic axis cannabinoids stimulate the activity of the dopaminergic neurons of the ventral tegmental area, which means that an elevation in dopamine levels is observed in the nucleus accumbens. It is highly likely that this action in the mesolimbic system plays a role in the reinforcing effects of the cannabinoids.

The CB1 receptors are expressed in a particular manner in the olfactory bulb, amygdala and piriform cortex and peripheral terminals, explaining the sympathetic inhibitory effects of the cannabinoids. Finally, activation of the CB1 receptors present in the hypothalamus-hypophyseal axis reduces circulating prolactin, LH (luteinizing hormone) and FSH (follicle stimulating hormone) levels, responsible for the synthesis of the sexual hormones (oestrogens and testosterone) and increases ACTH secretion (corticotrophin) and corticoid plasma levels.

In general all types of neurons express CB1 receptors. Although a pronounced CB1 receptor expression does appear to exist in the GABAergic neurons (inhibitors), the glutamatergic, cholinergic, peptidergic and catecholaminergic (excitatory) neurons also express cannabinoid receptors. Activation by the cannabinoids of the CB1 receptors causes a profound reduction in the release of neurotransmitters by the neuron carrying the CB1 receptors ("primary target"). However, circuit effects (especially disinhibition) mean that the cannabinoids can *in fine* trigger an excitation of certain neurons, for example dopaminergic neurons, which then make up a "secondary target".

Mechanisms of action for the cannabinoids can be proposed in the various target tissues

Animal studies have shown that the CB1 and CB2 receptors are expressed in the embryo at the pre and post-implantation stages as well as in the placenta. Anandamide levels in the

uterine wall are inversely proportional to receptivity of the uterus to implantation of the embryo. There are three spatiotemporal phases involved with the implantation of the embryo: pre-receptive (very high anandamide levels), receptive (low levels) and non-receptive (very high levels). It appears, then, that the cannabinoids determine a window of time for when an embryo can implant by synchronising differentiation of the blastocyte with the preparation of the uterus for the implantation stage. In addition, high anandamide concentrations prevent the migration of the blastocyte outside the appropriate sites. The effects of the cannabinoids on embryogenesis vary according to stage: among cells at stage 2, exposure of the egg to cannabinoids (even at low doses) disturbs blastocyte development. At the blastocyte stage, exposure to these same low doses promotes the differentiation and growth of the trophoblast. At the implantation stage of the embryo, very high doses of cannabinoids may compromise this step. The uterus, however, possesses systems for neutralising Δ9-THC (transformation of Δ9-THC into an inactive stereoisomer by cytochrome P450) at low doses. After perinatal exposure to Δ9-THC, no significant changes in cannabinoid receptor binding or in RNA expression of the CB1 receptor can be detected in the adult brain in mice.

Studies of vision in man have shown that Δ9-THC induces an increase in photosensitivity, and a deficit in the choice of response to very brief visual stimuli (< 100 ms), but causes no distortions in the detection of longer stimuli (> 100 ms) and does not affect detection of change in the light-dark phases. The CB1 receptor, in contrast to CB2, is expressed in the visual system both in the retina (rod cells, amacrine cells, and horizontal cells) and in the internal eye (cornea, iris, and ciliary body). Anandamide synthesis is about twice as high in the retina as in the rest of the brain. Cannabinoids produced a drop in intraocular pressure, an increase of which is the main cause of glaucoma in man. The mechanism remains hypothetical, but could involve a reduction in the formation of aqueous humour as well as an increased outflow of aqueous humour in the internal chamber of the eye (whence the therapeutic use of cannabinoids in the treatment of glaucoma).

The cardiovascular effects of Δ9-THC have been described for some time. It induces bradycardia and hypotension in animals and tachycardia in man. These effects are mediated by the CB1 receptors expressed in the central and peripheral nervous system (sympathetic axis). In the case of hypotension the effect of cannabinoids may also be direct, since the vascular endothelial cells express CB1 receptors and probably other specific anandamide receptors as well.

Findings from the animal model of bronchial constriction (rodent model of asthma) can be correlated with the observations made in humans. Exogenous Δ9-THC or locally released anandamide produces an effect dependent on the contractility of the bronchial muscle. In cases where the muscle is already contracted following irritation, cannabinoid ligands lead to inhibition of this contraction and thus to dilatation. Inversely, when the muscle is relaxed these cannabinoid ligands would induce constriction translated by an increase in bronchospasm, which are also observed in certain asthmatic patients using cannabis.

The majority of animal studies show that THC at very high doses exercises an immunosuppressor effect: it inhibits macrophage and lymphocyte function, resistance to infectious agents and cytokine production. In man, no study has unequivocally demonstrated that the cannabinoids have an immunomodulating effect. The use of tools such as selective antagonists and transgenic mice, in which the CB1 or CB2 genes have been inactivated, has shown that the cannabinoids can act as suppressors or stimulants of immune and inflammatory response according to the type of infectious agent involved and the immune cell in question.

The effect of the cannabinoids on cell growth or viability varies considerably. In vitro, the

cannabinoids can induce either a proliferation or a halt in growth and can trigger programmed cell death (apoptosis). These effects depend on the type of cell, concentration and type of cannabinoid ligand used and also on the treatment period. In animals Δ9-THC can have a proaptotic, direct antitumoral effect on glioma cells. Inversely, it has been demonstrated that it may also promote tumour growth (especially of tumours that do not express cannabinoid receptors) by virtue of its immunosuppressor effect.

Recommendations

The studies analysed show that significant advances have been made in recent years in the following areas of research: 1) the mechanism of action of the cannabinoids (of which Δ9-THC is the most representative active principle), 2) the location of the receptors to which cannabinoids bind in the central nervous system and other tissue sites, and 3) the detection of natural chemical substances in the brain acting on currently identified receptors.

Compared with these studies the epidemiological data available on the effects associated with cannabis appear far more limited. The detection of an association between cannabis use and a negative effect on health does not imply causation and does not tell us if use precedes the health problem. Observational studies of cohorts or experimental studies, which are the best context in which to clarify this, are few in the case of cannabis since it is an illicit psychoactive substance. Moreover, observational studies, which need a number of adjustments in order to take account of the different confounding factors, are few in number and often contradictory.

Animal studies raise problems of extrapolation across species, as particular attention should be given to routes of administration, to the forms of cannabis administered (active principle, plant extracts) and to the question of the equivalence between the doses administered in animals and consumption levels in man.

This summary, made on the basis of a critical analysis of the literature, has made it possible, nevertheless, to present data relating to cannabis consumption in France compared to other countries, to clarify the various immediate and long-term effects of cannabis in man with reference to the effects observed in animals, and to propose mechanisms of action for the cannabinoids that may be associated with the effects observed.

Information and prevention

INFORMATION AND PREVENTION CAMPAIGNS SHOULD TAKE ACCOUNT OF HOW USE DIFFERS WITH AGE AND GENDER

Under 18 years

Experimentation with cannabis essentially concerns the youngest populations. It is from the age of 15 years in particular that people experiment with cannabis. Thus lifetime prevalence of cannabis consumption in the CFES Health barometer 2000 ranges from 3.6 % in those aged from 12-14 years to 12 % in those aged 15-16 years. Their first encounter with the drug probably took place before the age of 15 years, but experimentation itself appears to coincide with starting secondary school. Cannabis is the first illicit substance that is available for experiment.

Studies suggest that the earlier initiation and consumption occur, the more likely use is to intensify rapidly, become persistent and lead to long-term harmful effects. According to the ESPAD survey, the prevalence of repeated consumption (10 times and more) in the past year increases from 2 % at the age of 14 years to 29 % at the age of 18 years in boys.

The lifetime prevalence of cannabis consumption is slightly higher in boys than in girls. In the ESCAPAD survey, 41 % of girls and 50 % of boys aged 17 years reported that they had used cannabis. According to the ESCAPAD survey, 60 % of boys and 45 % of girls aged 18-19 years have experimented with cannabis.

Boys remain more highly represented than girls at high levels of consumption. Thus, at the age of 17 years, boys are three times more likely than girls to have used cannabis at least 40 times in the past year (13.5 % versus 4.5 %, data from ESCAPAD 2000). And according to the ESCAPAD survey, 2.6 % of girls aged 17 years and 8 % of boys of the same age report consumption equal to or greater than 20 times a month.

From 19 to 25 years

Generally it is from the age of 19 years onwards that repeated use or polyuse may be observed. Thus prevalence of consumption equal to or greater than 20 times per month doubles in boys between the ages of 17 and 19 years (16 % versus 8 %, data from ESCAPAD 2000).

After the age of 25

Studies of the pathways taken by cannabis users show that stopping cannabis use applies to the great majority of adults after the age of 30-35. Epidemiological data collected by the Health barometer 2000 confirm that the prevalence of consumption in the course of the past twelve months reduces substantially as soon as ages above 25 years are reached (35.0 % in boys of 19 years versus 14.8 % in men of 25 to 34 years and 5.6 % in the 35-44 year age range).

The assumption by young adults of conventional social roles, in particular marriage or the arrival of children makes it more likely that they will stop using cannabis.

TARGET INFORMATION AND PREVENTION CAMPAIGNS ON IMMEDIATE OR LONGER-TERM HEALTH RISKS

Immediate or short-term effects

Using cannabis has an irreversible adverse effect on certain psychomotor and cognitive abilities. Doses inducing drowsiness, euphoria and feelings of wellbeing are already associated with deterioration in temporal perception, short-term memory disorders and an inability to divide attention among simultaneous tasks. When cannabis use is higher, language disorders and impaired motor co-ordination may appear, as well as dysphoria. These changes may last up to 24 hours.

The other somatic signs associated with cannabis consumption are minor ones: increased heart rate and cardiac output, vasodilatation and eye irritation and gastrointestinal disorders. There has never been any reported case of death after isolated acute intoxication, which is in accordance with the low levels of expression of the cannabinoid receptors in the cerebral centres controlling respiratory and cardiovascular functions.

Acute psychiatric complications, such as panic attack or depersonalisation syndrome, have been observed in certain subjects. These complications could lead to stopping consumption. Exceptionally, cases of cannabis psychosis (similar to acute delirious outbursts, but with more heteroaggressive behavioural disorders, visual hallucinations and depersonalisation) have been described in adults without premorbid disorders. An analysis of the cases reported shows that these clinical pictures occur after a recent increase in cannabis use.

Certain studies report that cannabis consumption promotes the adoption of high-risk sexual behaviour (multiple partners, not using condoms).

Long-term effects of repeated use, daily use or multiple daily use

The repeated use of cannabis, defined here as use more than 10 times in the past year, applies to 29 % of boys aged 18 years and 14 % of girls of the same age, interviewed in 1999 in the context of an ESPAD survey. According to the ESCAPAD survey, 16 % of boys aged 19 years have used cannabis at least 20 times per month.

This level of consumption can lead to an increased risk of dependency (according to DSM-IV criteria). This kind of dependency is generally considered not to be accompanied by physiological dependency, although a phenomenon of tolerance is observed in chronic users and a weak withdrawal syndrome is also described.

American studies estimate the proportion of subjects in the general population presenting a risk of cannabis dependency to be about 5 %, as testified by the presence of a specified number of dependency criteria defined by DSM-IV. In sub-groups of user subjects this prevalence would be about 10 %. Few surveys have in fact investigated the correlations between risk of dependency and the quantity or frequency of cannabis consumption. It is the 15-24 age that appears to be at the highest risk.

Long-term somatic effects of cannabis consumption are likely to appear in adult users. Several studies (analysis of case reports, case control studies) thus suggest an association between the occurrence of bronchopulmonary or upper airway cancer and cannabis consumption with or without that of tobacco. Cannabis use could shorten the latency period for the development of bronchial cancer since it is reported in smokers aged less than 45 years.

INFORMATION AND PREVENTION CAMPAIGNS SHOULD TAKE INTO CONSIDERATION INDIVIDUAL VULNERABILITY FACTORS FOR ABUSE

Personality traits, personality disorders

Studies associate certain personality traits (low self-esteem, difficulties in facing up to events, difficulties in solving interpersonal problems) or of temperament (sensation seeking, low risk avoidance) with an increased risk of abuse or dependency on psychoactive substances, including cannabis. The prevalence of personality disorders (borderline, antisocial) is greater in subjects who abuse or are dependent on cannabis than in the general population. These personality traits and disorders are not specific to cannabis abuse but it is important to be alert to them.

Early tobacco smoking and alcohol use

Certain behavioural disorders appear to be associated with repeated cannabis use: regular consumption of other psychoactive substances such as tobacco and alcohol (including seeking alcoholic intoxication). The connections found are always stronger in girls than boys. Accordingly the odds ratio for seeking alcoholic intoxication in the case of daily cannabis use is 11.8 in schoolgirls as opposed to 7.3 in schoolboys. Early tobacco smoking is also a risk factor for cannabis abuse. Initiation to cannabis when it is early is most often found associated with the presence of behavioural disorders in girls.

Problems of parental addiction

A family history of alcoholism or drug-dependency is a well-identified risk factor. The consumption of psychoactive drugs by the parents is very strongly associated with consumption of these drugs in their children. It has been demonstrated that boys whose fathers are at risk in connection with the use of psychoactive substances have a markedly higher risk of cannabis abuse than boys whose fathers have no addiction problems.

Studies in genetic epidemiology show that the relatives of subjects presenting a risk of addiction are at a higher risk themselves of having a disorder connected with substance abuse including cannabis. The weight of genetic factors is more significant for abuse and dependency than for straightforward use.

INFORMATION AND PREVENTION CAMPAIGNS SHOULD TAKE INTO ACCOUNT PARTICULAR SITUATIONS AND DISEASES

Driving a car, high-risk professions

The psychoactive effects of cannabis consumption last on average 2 to 10 hours, according to the dose taken and individual sensitivity. Certain of these effects, detected in the course of experimental studies, appear incompatible with driving cars: slowed reaction time, reduced ability to control a path, poor appreciation of time and space and impaired responses to emergencies. As it is young adults in the same age range as those who frequently use cannabis who are learning to drive, it may be worth including information on the effects of cannabis in the Highway Code.

Cannabis use is, for the same reasons, incompatible with work in certain positions involving taking responsibility for the safety of others, described as being "high-risk", because of its psychoactive and disinhibiting properties.

Patients suffering from mental disorders

Patients suffering from certain mental disorders use or have used cannabis more frequently. This consumption is often a factor connected with a poor prognosis, as has been demonstrated in bulimic and schizophrenic patients. The former show an aggravation in the global effects of the disorders connected with cannabis consumption. In the latter cannabis use plays a partial role in their poor therapeutic compliance, more frequent recourse to hospitalisation and an increased transition to suicidal acts. Some of these subjects are high consumers of cannabis as well of other toxic substances.

Pregnant or lactating women

In cases of maternal cannabis consumption during pregnancy Δ9-THC levels in the foetal blood are at least equal to those present in the maternal blood. Repeated and substantial cannabis consumption during pregnancy is associated in several studies with effects on the behaviour of the neonate (increased trembling, decreased visual response to light stimuli, reduction in the strength of crying, deterioration in sleep and increased impulsivity), which appear to regress during the first months of life. Two prospective studies, however, note that some of these disorders persist. Three case control studies have reported an increased risk of cancer (acute non-lymphoblastic leukaemia, astrocytoma or rhabdomyosarcoma) in children born to user mothers. Although these results need to be confirmed they are still worth

reporting.

By virtue of its lipophilia Δ9-THC passes into the mother's milk where its concentration could be at least as high as in the blood. Although no study to date has measured the harmful effects of maternal cannabis users breast feeding babies, information on potential risks should be given to mothers who hope to breast feed their child.

Research development

TOOLS ADAPTED TO EPIDEMIOLOGICAL SURVEYS

The available surveys in Europe, North America, Australia and New Zealand are concerned with the consumption of several psychoactive drugs and not only cannabis consumption. These surveys are performed by random survey of samples representative of the populations concerned. The amounts used are rarely quantified and this omission considerably hampers the interpretation and comparison of studies. Furthermore, few studies are interested in high frequencies of consumption. Daily consumption, for example, is only rarely reported, and in certain studies it is associated with an increased risk of cannabis dependency.

The expert group recommends developing methods of standardising tobacco, alcohol and cannabis consumption, which include dose and frequency of use. A standardised approach of this kind should make it possible to characterise moderate and heavy use and use likely to lead to harmful effects, according to the drugs employed. The expert group recommends the validation of tools in France for quantifying use and for identifying dependency, which can be used in epidemiology, in general medicine and by social services and similar parties, through the establishment of a gold standard based on the kind of questionnaire that has already been experimented with in other countries.

The studies should provide information on the distribution by age and gender of occasional, regular, abusive or dependent users and enable follow-up of the course of prevalence over time. Questionnaires should include use of other drugs according to age range.

STUDIES ON FACTORS ASSOCIATED WITH REPEATED CONSUMPTION

Several studies have shown that sensation seeking was a predictor of use and abuse of psychoactive substances in general and of cannabis in particular. The reasons for this association remain unknown and may be the result of both genetic and environmental factors. This two-fold contribution to covariation between risk taking and cannabis use has been evaluated in adolescent twins. Levels of consumption, however, were not evaluated. The expert group recommends clarifying the relationships between cannabis consumption and personality traits (impulsivity, sensation seeking, violence), and the problems of adolescence, and investigating the potential effect of factors connected with gender in this consumption.

The majority of studies emphasizes that cannabis consumption is often associated with that of alcohol. Certain studies put forward the hypothesis that alcohol use could influence expectations in relation to cannabis, and thus its use and vice versa. The expert group recommends studying the nature of the relationship between alcohol and cannabis consumption, in particular in relation to the search for intoxication. Furthermore tobacco consumption, being frequently associated, could accentuate that of cannabis. The expert

group recommends research into factors that could make possible a transition from one drug to another, by performing not only longitudinal epidemiological studies, but also clinical or experimental studies in animals, in the context of multidisciplinary collaboration.

RESEARCH INTO THE NATURE OF CONNECTIONS BETWEEN CANNABIS ABUSE AND THE PRESENCE OF MENTAL DISORDERS

The consumption of psychoactive substances, in particular alcohol and cannabis, is frequent in patients presenting mental disorders. This should then be systematically researched in these patients. A survey performed in France reports that 36 % of hospitalised schizophrenic subjects are, or have been, dependent on cannabis. The association between schizophrenic disorders and cannabis dependency could be an expression of a common vulnerability, whether genetic or environmental in origin. The expert group recommends studying the potential interactions between cannabis, the endocannabinoid system and schizophrenia. It recommends pursuing studies on the genetic polymorphisms of cannabis receptors and the enzymes of endocannabinoid metabolism with the aim of studying vulnerability factors.

EVALUATING THE MANAGEMENT OF PATIENTS WHO ABUSE OR ARE DEPENDENT ON CANNABIS

The number of cannabis users managed by the health and social services has been on the increase since 1987 (annual data from DREES). In 1999, cannabis consumption was at the root of 15 % of recourse to medical care in France.

The expert groups recommends evaluating different strategies for managing users according to the level of consumption and setting up a coherent pilot system adapted to adolescents: brief periods of medical management in order to evaluate associated comorbidities and management by specialist teams for users who are dependent on cannabis or polydependent.

STUDYING THE CORRELATION BETWEEN EFFECTS AND Δ9-THC BLOOD CONCENTRATIONS

The data in the literature indicate that significant Δ9-THC blood concentrations (several ng/ml) are generally accompanied by pharmacological effects without it being possible, despite this, to establish a dose-response relationship. Only one study proposed a mathematical model which, by taking blood levels of Δ9-THC and of its two metabolites (11-OH-Δ9-THC and Δ9-THC-COOH) into account, established the cannabis influence factor making it possible to confirm or discount the presence of pharmacological effects. The expert group recommends that research be encouraged to estimate the validity of this kind of score which could make it possible to classify user subjects as being "under the influence" (score > 10) or not (score = 10) in surveys seeking to assign responsibility for road accidents.

The effects of cannabis, studied on the basis of specific tasks connected with driving a car show that impairments of memory, attention and psychomotor control may compromise certain aspects of driving. The expert group recommends that research be carried out in order to explore the temporal relationships between cannabis consumption and its cognitive and psychomotor effects and the factors that could influence this relationship (doses, individual factors). Various studies show that the combined effects of alcohol and cannabis produce a deterioration in driving and a higher risk of accidents than alcohol alone. The expert group recommends finding out whether a synergic effect with alcohol exists, taking into account the difference in chronology of effects after consumption.

VALIDATION OF STRATEGIES TO IDENTIFY CANNABIS CONSUMPTION THROUGH LABORATORY TESTS

Urine currently constitutes the only biological medium that can be used for mass identification of cannabis consumption. Saliva could be a medium of choice making it possible to confirm recent cannabis use, unlike urine, which can provide information only on the time elapsed between consumption and test. The Δ9-THC detected in the saliva originates essentially from a phenomenon of buccadental sequestration on inhalation. The expert group recommends developing a system appropriate to this biological medium, which would be worthwhile because it is particularly easy to collect in the context of mass screening.

STUDIES ON THE CONSEQUENCES OF EXPOSURE IN UTERO

Cannabis consumption during pregnancy is associated with a number of effects on the behaviour of the neonate. The expert group recommends conducting a follow-up study of children whose mothers used cannabis during pregnancy, in order to identify and quantify the effects of this consumption on the child's future. A study of this kind should take into account all the environmental factors likely to influence the behaviour of children and to constitute confounding factors. Animal data, which have detected a teratogenic effect and an embryotoxicity from Δ9-THC, have been obtained after administration of very high doses using a mode of administration unrelated to human cannabis consumption. The expert group recommends that research be conducted with a route of administration and doses that would enable a real comparison with the situation in man.

The group also recommends that the proportion of pregnant women using cannabis be estimated in France. Three case control studies have detected an increased risk of cancer (acute non-lymphoblastic anaemia, astrocytoma or rhabdomyosarcoma) in children born to user mothers. Because the consequences on health described, these results need to be confirmed.

Furthermore, a study comparing data on cannabis consumption (dose and duration) in women of child-bearing age and in the period leading up to conception would make it possible to provide information on the effects of cannabis consumption on fertility. The highly lipophilic Δ9-THC passes readily into the mother's milk. The expert group recommends that a study be performed in order to evaluate the levels transferred into the mother's milk.

STUDIES ON THE LONG-TERM EFFECTS OF CANNABIS

Any evaluation of cancer risk connected with cannabis consumption should take into account, at least in European studies, the mode of consumption associated with tobacco. Initial epidemiological results suggest, however, that cannabis consumption alone, that is to say in the form of grass, is associated with an increased risk of upper airways cancer. The expert group recommends performing epidemiological research in France and Europe on the development of cancers connected with chronic cannabis consumption or with exposure in utero. It also recommends pursuing research into the mutagenic and carcinogenic potential of the active principle (Δ9-THC) and cannabis smoke. The expert group recommends studying the induction by Δ9-THC of the enzymes involved in the metabolism of

carcinogenic substances, in particular of cytochromes P450 and their impact on lung tissue.

The search for persistent cognitive effects in chronic users has not provided any very convincing results to date. Nevertheless the question is important, for adolescent subjects in particular, since this cognitive deterioration could have consequences for memory, the acquisition of knowledge and educational achievement. Could the amotivational syndrome observed at times in clinical practice be connected with impairments of this kind? The expert group recommends developing studies making it possible to investigate the existence of cognitive disorders connected with chronic cannabis consumption. It is probable that these studies require particularly large populations so that limited effects are detected. The dose-response relationship and the reversibility or persistence of disorders are essential aspects of the problem.

FUNDAMENTAL STUDIES ON THE ENDOCANNABINOID SYSTEM

The pharmacological effects of the cannabinoids are mediated by an endogenous cannabinoid system composed of neurochemical substances and receptors (CB1 and CB2). However, the experimental studies analysed did not enable clarification of all the effects of the cannabinoids by the mediation alone of currently identified receptors. Endogenous ligands other than anandimide and 2-arachidonoyl-glycerol may exist. The expert group recommends encouraging research into all the endogenous cannabinoid system (receptors, endogenous ligands). It recommends that the functions of the cannabinoid system be explored, study of which could make it possible to decode the mechanisms brought into play in the various effects induced by Δ9-THC. This research should benefit from the development of knock-in or knock-out animal models appropriate to the different components of the endogenous system. It would be necessary to think in terms of collaboration with those pharmaceutical companies that have developed selective Δ9-THC antagonists to CB1 and CB2 receptors.

An effort should be made to evaluate the importance of these systems in man using the latest techniques in non-invasive medical imaging. To this end, it is necessary to promote the study of the cerebral structures involved in the acute and chronic effects of the exogenous cannabinoids. As soon as the pharmacopoeia permits, special value should be given to the effects of modulating agents of the endocannabinoid systems (transporter, degradation enzyme, receptor). Individual variations should be taken into account with the aim of assessing the significance of physiological differences in the genesis of excessive cannabis consumption.